Sustainable pathways to bio-based amines via the 'hydrogen borrowing' strategy

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Chapter 4

Amination of *β*-hydroxyl acid esters *via* cooperative catalysis: enabling access to bio-based *β*-amino acid esters

While in Chapter 3 natural amino acids were used as a starting material for the construction of valuable cyclic amines, the production of amino acids and its derivatives, the key bio-based building blocks for the synthesis of multiple pharmaceutically active compounds, is a major focus in the present chapter. A robust and versatile method for obtaining β-amino acid esters by direct amination of β-hydroxyl acid esters catalysed by cooperative catalytic system, comprises a combination of a homogeneous ruthenium catalyst and an appropriate Brønsted acid additive, via the borrowing hydrogen methodology is reported. This method allows for the direct amination of esters of 3-hydroxypropionic acid, a top value-added bio-based platform chemical, opening an entirely new and remarkably simple route to access β-amino acid esters from a range of renewable polyols including sugars and glycerol.

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4.1 Introduction

β-Amino acid esters are privileged structural motifs in a wide variety of biologically active compounds[1] and indispensable building blocks for the synthesis of *β*-peptides[2,3] and *β*-lactam antibiotics.[4,5] Owing to their importance, numerous synthetic pathways have been developed, already starting from the beginning of the 20th century, for the construction of racemic *β*-amino acids and derivatives (**Figure 4.1A**). Racemic *β*-amino acid moieties can be readily constructed by classical stoichiometric methods including the nucleophilic attack of cyanide on an *α*-haloester followed by nitrile reduction (**Figure 4.1A**, pathway **a**), the Michael addition of amines to *α*,*β*-unsaturated esters (**Figure 4.1A**, pathway **c**), the Mannich reaction of a malonic- or cyanoacetic ester, ammonia and aldehyde (**Figure 4.1A**, pathway **d**), the Knoevenagel condensation of a cyanoacetic ester with an aldehyde (**Figure 4.1A**, pathway **f**); however, these approaches frequently involve the use of toxic reagents and generate significant amounts of waste (**Figure 4.1A**).[6–9] While for the synthesis of chiral *β*-amino acid moiety, asymmetric hydrogenation is clearly the most powerful and intensely studied catalytic methodology either using chiral ligands or chiral Brønsted acid auxiliaries.[10–12]

An alternative elegant way of constructing *β*-amino acid scaffolds would be *via* the direct coupling of *β*-hydroxyl acids or esters with amines. Such transformation would proceed without the formation of any waste, and may also be, in the future, carried out in an enantioselective manner; however, it has not been reported to date. Nonetheless, for targeting pharmaceutical compounds as well as functional materials and polymers, a clean synthetic approach would be certainly preferred (**Figure 4.1B**).[13] Moreover, such atom-economic method would enable the unprecedented, direct catalytic amination of important bio-based *β*-hydroxyl acid ester building blocks.

3-Hydroxypropionic acid (3-HP) has been identified as one of the top twelve value-added renewable platform chemicals.[14–16] Its structure comprises two functional groups, namely a carboxyl group and a *β*-hydroxyl group, making it a perspective building block for the synthesis of a variety of high value-added chemicals including 1,3-propanediol, acrylic acid, acrylamide, acrylonitrile, propiolactone, malonic acid, homopolymers, and heteropolymers. [14–18] These 3-HP derivatives, being the starting material for the preparation of polymers, have found an application in the field of coatings, textiles, paper-making, sealants, adhesives. Interestingly, among the existing chemo- and biocatalytic routes for the conversion of 3-HP and its esters to chemical intermediates[14–17], the direct and selective amination of the (3-HP) alcohol moiety has not been recognized or achieved yet. In recent years, much attention has been devoted to the development of industrially relevant, scalable methods for the production of 3-HP and its ethyl ester from the renewable polyols (glucose, glycerol) (**Figure 4.1C**).[15,18–20] Thus realizing the above mentioned one-step catalytic amination would create access to valuable synthetic *β*-amino acid esters from diverse renewable sugar feedstocks, including non-edible lignocellulosic agricultural or forestry waste materials[21] as well as glycerol, the major byproduct of biodiesel production.[22]

An attractive method for carrying out the desired catalytic C-N bond formation is the direct amination of alcohols *via* the borrowing hydrogen approach (**Figure 4.3A**).[23–26] Despite

tremendous progress,[27–30] methodology development in the field has generally overlooked the use of potentially strongly coordinating substrates and no examples on β-hydroxyl acids or derivatives have been reported. In the recent pioneering work, Yan and co-workers have reported the first example of catalytic amination of biomass-derived α-hydroxyl acids with ammonia, using heterogeneous Ru-based catalysts.[31] Based on tandem biocatalysis/ heterogeneous catalysis approach, this work pioneered sustainable pathways from sugars to α-amino acids, comparable with the well-established microbial cultivation processes, and therefore opening the way to the perspective production of high-value proteins from agricultural wastes *via* chemical routes. Earlier, Beller described the first example of catalytic amination of α-hydroxyl amides with amines using $[Ru_3(CO)_{12}]$/DCPE.[32] This study also included methyl 2-hydroxypropanoate as substrate, but only the corresponding α-amino amide was formed, indicating low ester functional group tolerance under the reported conditions. Herein, we set to realize the catalytic amination of β-hydroxyl acid esters, including esters of the bio-based 3-HP.

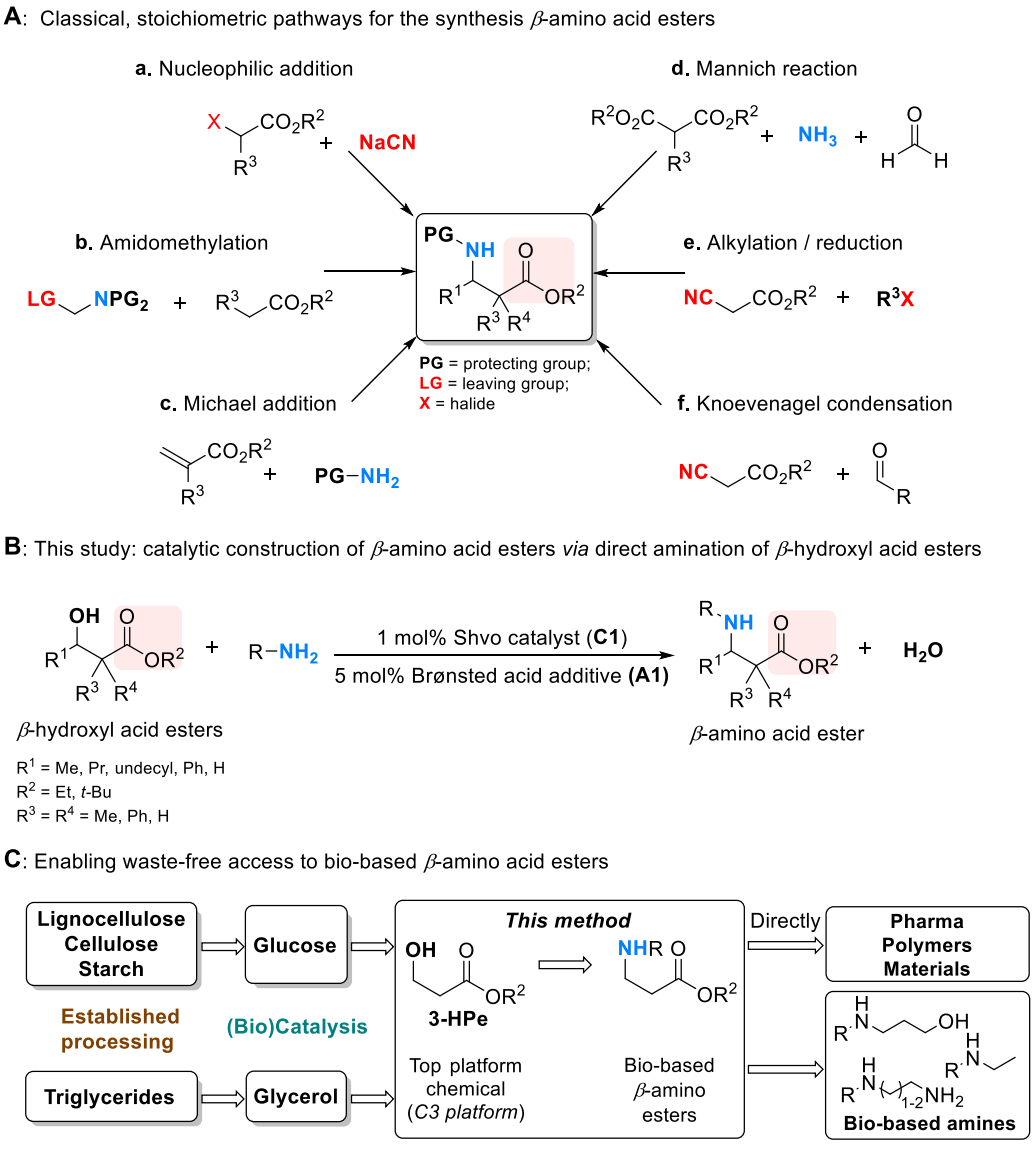


Figure 4.1: Strategies to access β-amino acid esters. **(A)** Classical, stoichiometric pathways; **(B)** Novel catalytic method for *N*-alkylation of β-amino acid esters *via* the hydrogen borrowing

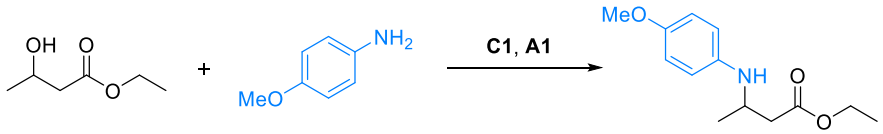
strategy established here; **(C)** New route to bio-based *β*-amino acid esters from renewable polyols and subsequent transformation to valuable bio-based building blocks.

4.2 Results and discussion

4.2.1 Establishing the novel catalytic amination of *β*-hydroxyl acid esters

This transformation is expected to be challenging because of side reactions such as intermolecular transesterification, partial ester hydrolysis or *β*-amino acid amide formation. Moreover, the *β*-hydroxyl acids or corresponding *β*-ketoacid/ *β*-iminoacid intermediates (**Figure 4.3A**) may form chelating complexes with the homogeneous catalyst, blocking coordination sites necessary for efficient catalysis.[33–35] Therefore, the desired transformation requires a robust catalytic system with great functional group tolerance. Very recently, we developed the first *N*-alkylation of unprotected *α*-amino acids with alcohols using the Ru-based Shvo's catalyst.[36] This robust and base-free catalytic system appeared as excellent starting point for the synthesis of *β*-amino acid esters from *β*-hydroxyl acid esters and various amines (**Figure 4.1B**). We started our investigation using ethyl 3-hydroxybutanoate and *p*-anisidine, with the Ru-based Shvo's catalyst. Very poor substrate conversion was seen even at 120 °C, and the desired product was observed only in traces beside a small amount of imine (**Table 4.1**, entry 1).

Table 4.1: Establishing reaction conditions for the synthesis of ethyl 3-((4-methoxyphenyl)amino)butanoate (**3aa**) from 3-hydroxybutanoate (**1a**) and *p*-anisidine (**2a**).



1a **2a** **3aa**

Entry	**C1** [mol%]	Additive [mol%]	Temp. [°C]	Solvent	Conv. [%]	Sel. **3aa** [%]
1	1	-	120	Toluene	17	7
2	**1**	**A1 (5)**	**120**	**Toluene**	**>99**	**>99(87)**
3	1	**A1** (5)	100	Toluene	21	21
4	1	**A1** (5)	110	Toluene	47	47
5	0.5	**A1** (5)	120	Toluene	51	51
6	-	-	120	Toluene	0	0
7	-	**A1** (5)	120	Toluene	0	0
8	1	**A1** (5)	120	CPME	67	67
9	1	**A1** (5)	120	1,4-Dioxane	25	25
10	1	**A1** (5)	120	CH_3CN	0	0
11	1	**A1** (5)	120	THF	19	19
12[a]	1	**A1** (5)	120	Toluene	>99	85
13[b]	1	**A1** (5)	120	Toluene	76	63

General reaction conditions: General Procedure, 1 mmol of **1a**, 0.5 mmol of **2a**, 0.5-1 mol% Shvo's complex (**C1**), 5 mol% additive (**A1**), 2 mL of solvent, 18 hours, 100-120 °C, under argon, isolated yields in parentheses. Conversion and selectivity were determined by GC-FID. [a] 1.5 equiv. of **1a** was used. [b] 1 equiv. of **1a** was used.

In view of the possible side reactions and with the aim to keep low catalyst loading and mild reaction conditions, we explored alternative ways of enhancing reactivity. Achiral and chiral Brønsted acids have emerged as powerful tools in a wide variety of transformations.[34-42] In particular, the use of Brønsted acids in combination with transition metal catalysts have shown beneficial in hydrogenation reactions, such as Ru[37], Ir[38] and Fe-catalysed hydrogenation of imines[39] as well as reductive amination.[40] Interestingly, recently Zhao has demonstrated the enantioselective amination of alcohols by a cooperative catalytic system comprising an iridium complex and an appropriate chiral phosphoric acid, *via* the borrowing hydrogen methodology.[41] Thus, inspired by the remarkable achievements in cooperative transition-metal and Brønsted acid catalysis[12,37–44] we have applied diphenyl phosphate (**A1**) as a Brønsted acid additive, assuming that it may facilitate imine reduction by bifunctional catalysis, and in addition potentially enhance imine formation by activation of the carbonyl in the nucleophilic attack by the amine, both steps involved in the borrowing hydrogen cycle (**Figure 4.3A**).

Indeed, perfect (>99%) conversion and selectivity (>99%) were achieved using diphenyl phosphate (**A1**) and **C1** at 120 ºC (**Table 4.1**, entry 2). The high level of product selectivity shows that under these carefully selected conditions, the tendency for *β*-elimination is overcome in favour of dehydrogenation and imine formation. Further lowering the reaction temperature or catalyst amount have not proven beneficial (**Table 4.1**, entries 3-5). A blank reaction in the absence of catalyst and additive, or just with **A1**, gave no detectable conversion (**Table 4.1**, entries 6-7). Solvent screening showed moderate success (**Table 4.1**, entries 8-11). Decreasing the amount of alcohol to 1.5 and 1 equivalents (**Table 4.1**, entries 12-13) gradually declined conversion, therefore, for future study an alcohol: amine ratio of 2:1 was kept.

Additional *in situ* 1D and 2D ^{1}H NMR and GC-FID and GC-MS studies of the amination of ethyl 3-hydroxybutanoate (**1a**) and ethyl 3-hydroxy-2,2-dimethylpropanoate (shown later, **1e**) with *p*-anisidine (**2a**) in presence of **C1** with/without diphenyl phosphate additive (**A1**) were performed. All key intermediates, such as the corresponding imine (**3'ea**), enamine (**3''aa**) and ketone (**1'a**), were detected that affirmed the proposed borrowing hydrogen mechanism **Figure 4.3A**.

Deuterium incorporation experiments using the separately prepared, selectively D-labelled key substrate ethyl 3-hydroxyhexanoate-3-d (**1b-d1**) and applying the simpler substrate, benzyl alcohol-α,α-d_2[30] (**Figure 4.2A-B**) showed deuterium transfer from the substrate to the amine product in accordance with a borrowing hydrogen mechanism.

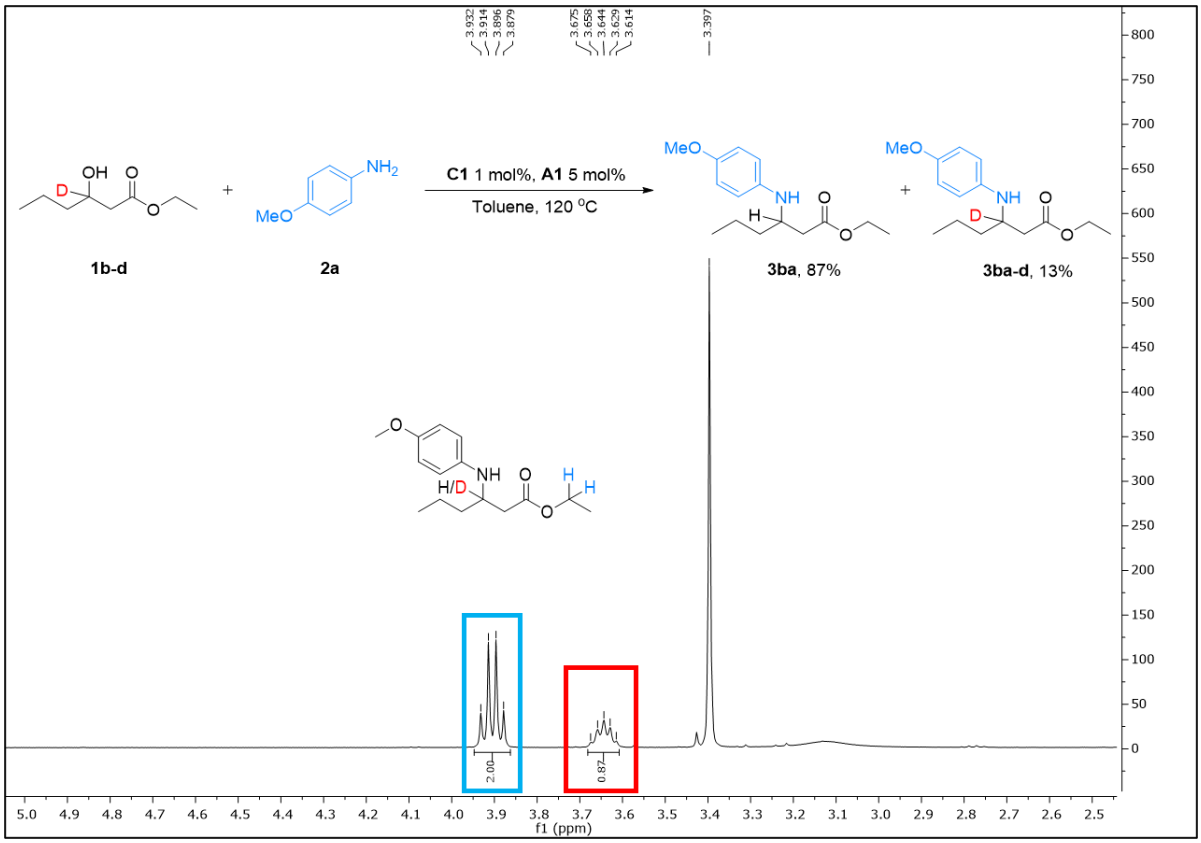


Figure 4.2: **(A)** Deuterium incorporation experiment using **1b-d1** as a substrate.

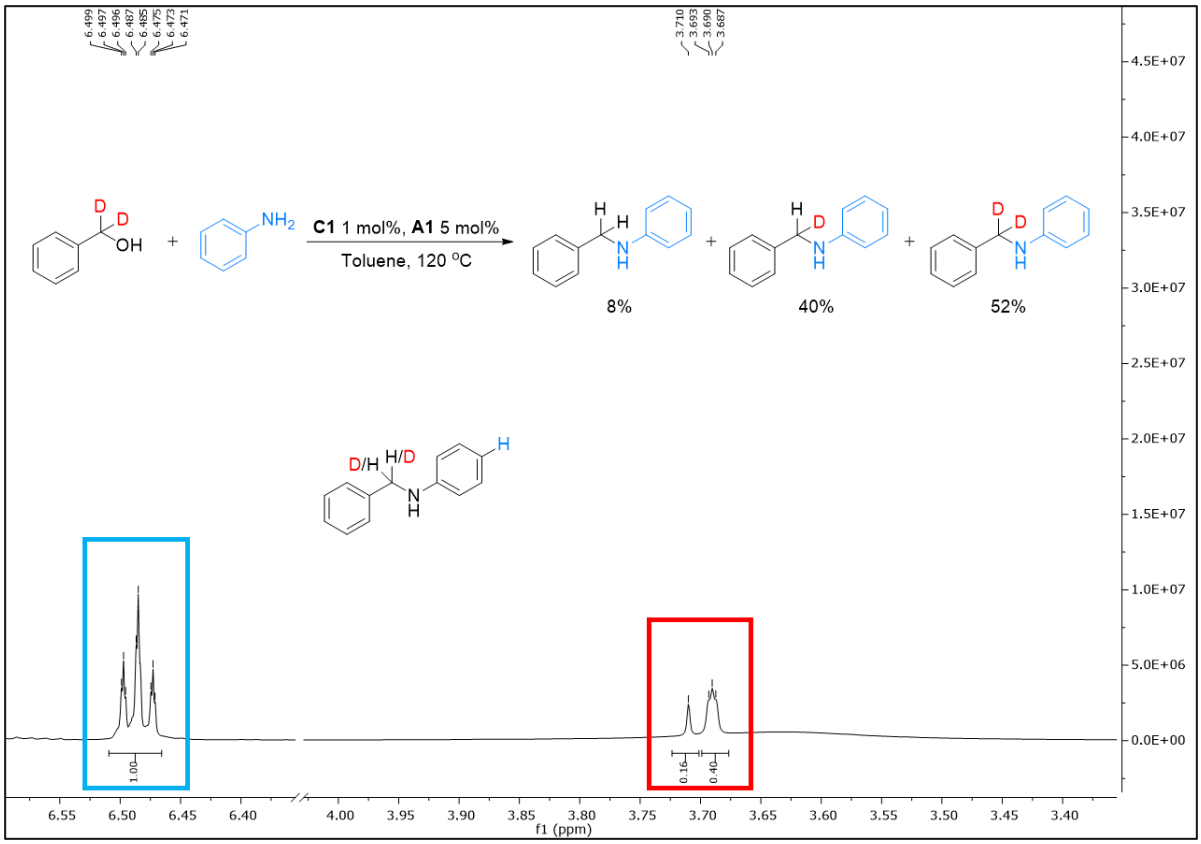


Figure 4.2: **(B)** Deuterium incorporation experiment using benzyl alcohol-α,α-d_2 as a substrate.

Furthermore amination of chiral alcohols, namely ethyl (*S*)-3-hydroxybutyrate (**(*S*)-1a**) and ethyl (*R*)-3-hydroxybutyrate (**(*R*)-1a**) with *p*-anisidine (**2a**) lead to racemic amine products, as further evidence for the existence of the borrowing hydrogen pathway over an ionic mechanism.[45] The former pathway proceeds through loss of the chirality of the substrate alcohol by its dehydrogenation to furnish the corresponding achiral carbonyl compound.

4.2.2 Role of the Brønsted acid additive

Gratifyingly, additional ^{1}H NMR experiments also revealed the existence of an imine (**3'aa**) - enamine (**3''aa**) equilibrium and the shift of this equilibrium in the presence of additive **A1** toward the more reactive imine **3'aa** form (**Figure 4.4**).

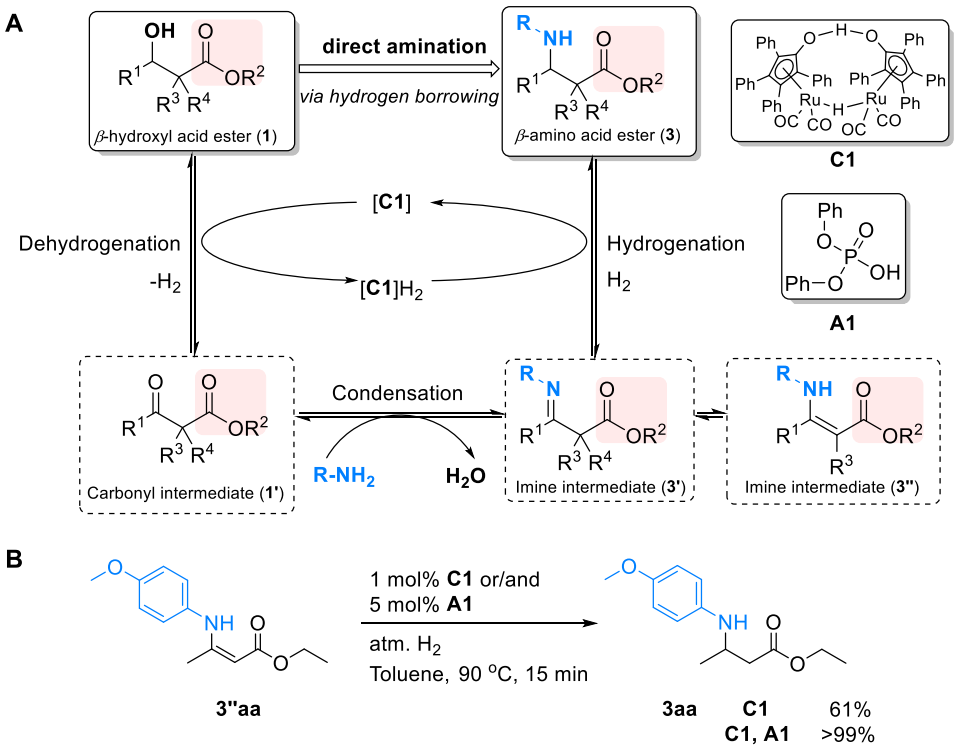


Figure 4.3: Catalytic amination of the *β*-hydroxyl acid esters *via* the hydrogen borrowing strategy. **(A)** Proposed mechanism; **(B)** Hydrogenation of **3''aa** in the presence of Shvo's catalyst (**C1**) and/or diphenyl phosphate additive (**A1**). Reaction conditions: atm. H_2, 90 °C, 15 min.

More experiments were conducted to further elaborate on the role of the acid additive in the crucial imine formation and imine hydrogenation steps of the hydrogen borrowing cycle. Reactions between ketone (**1'a**) and *p*-anisidine (**2a**) with and without additive **A1** were conducted, showing a beneficial effect of the additive on the imine formation step, as expected: full conversion and >99% selectivity were achieved with **A1** while 64% conversion and 22% selectivity were seen without **A1**. Conducting this reaction step separately also shows the advantage of the full borrowing hydrogen cycle that starts from the alcohol directly and results in the stable amine product. Advantageously, in this case, the ketone and apparently labile imine intermediates are kept at low concentration, thereby minimizing the possibility for side

reactions. Next, we examined the hydrogenation of the enamine (**3''aa**), which was obtained *via* synthetic procedures[46], in the presence of 1 mol% Shvo's catalyst (**C1**) with/without acid co-catalyst (**A1**) (**Figure 4.3B**). The excellent, 99% **3aa** yield in the presence of **A1** compared to the lower 61% **3aa** yield obtained in the absence of **A1** underscores its beneficial effect in the rate of imine hydrogenation.

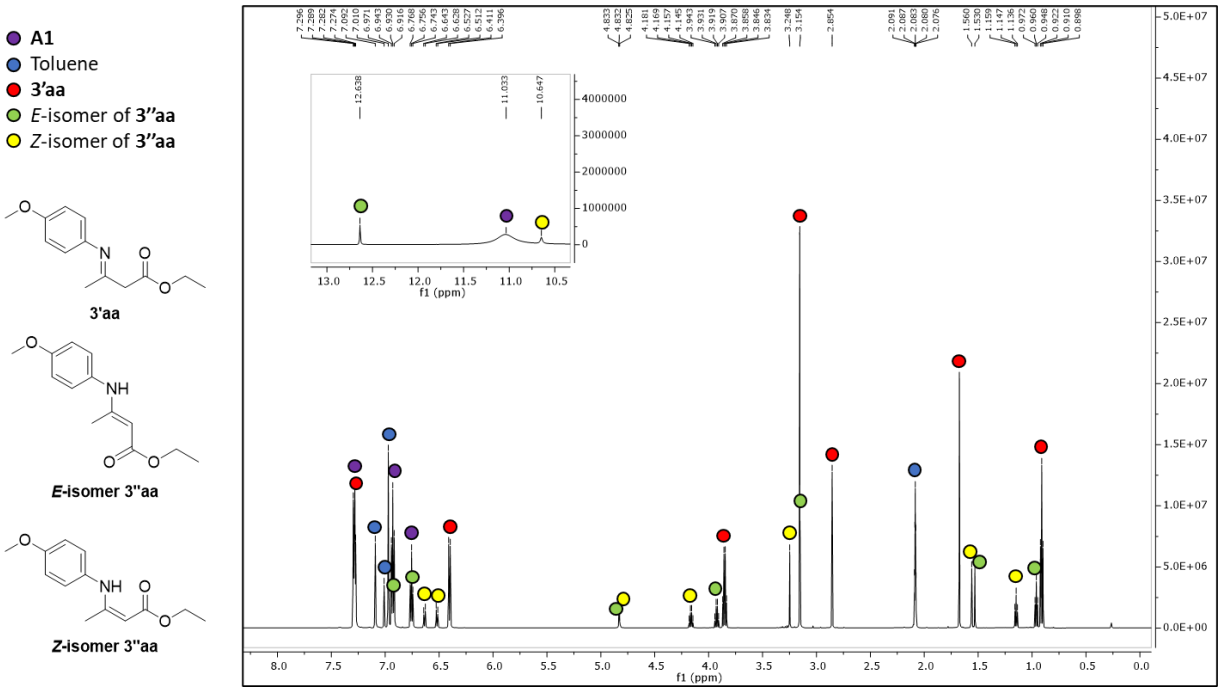


Figure 4.4: ^{1}H NMR spectrum of the 3-(4-methoxyphenylamino)-but-2-enoic acid ethyl ester (**3''aa**) in presence of diphenyl phosphate additive (**A1**) showing the existence of an imine-enamine equilibrium.

To further understand how this rate enhancement occurs, and to gain more insight into a possible cooperative catalysis by **C1**-**A1**, *in situ* ^{31}P NMR spectroscopic investigations using toluene-d_8 as solvent at 60 °C were conducted (**Figure 4.5A**).

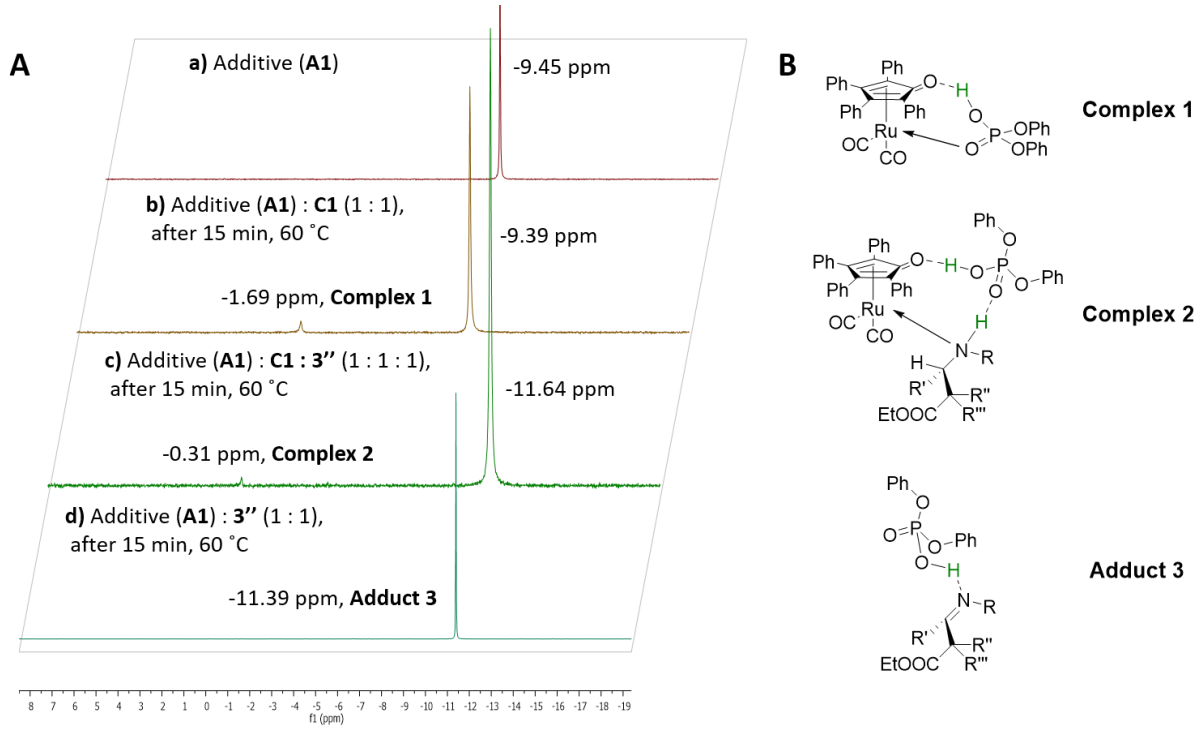
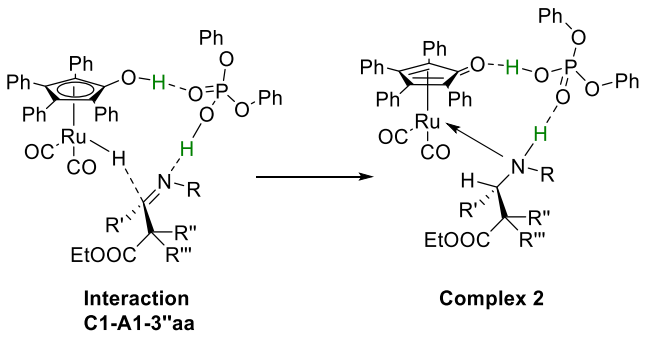


Figure 4.5: **(A)** *In situ* ^{31}P NMR spectra of diphenyl phosphate additive (**A1**), Shvo's complex (**C1**) and 3-(4-methoxyphenylamino)-but-2-enoic acid ethyl ester (**3''aa**) in different ratios: **a)** diphenyl phosphate (**A1**, -9.45 ppm); **b)** 1:1 mixture of diphenyl phosphate (**A1**) and Shvo's catalyst (**C1**) (formation of possible **Complex 1** at 1.69 ppm); **c)** 1:1:1 mixture of diphenyl phosphate (**A1**), Shvo's catalyst (**C1**) and 3-(4-methoxyphenylamino)-but-2-enoic acid ethyl ester (**3''aa**) (formation of possible **Complex 2** at -0.31 ppm and **Adduct 3** at -11.64 ppm); **d)** 1:1 mixture of diphenyl phosphate (**A1**) and 3-(4-methoxyphenylamino)-but-2-enoic acid ethyl ester (**3''aa**) (formation of possible **Adduct 3** at -11.39 ppm); **(B)** Proposed adducts involved in cooperative catalysis supported by ^{31}P NMR investigation.

Initially, the spectrum of pure diphenyl phosphate (**A1**) was recorded (**Figure 4.5A-a**) displaying a typical chemical shift at -9.45 ppm. Next, the mixture of Shvo's complex (**C1**) and diphenyl phosphate (**A1**) (1:1) at 60 °C after 15 minutes (**Figure 4.5A-b**) was recorded in order to assess possible interaction between additive and catalyst. Indeed, beside the signal of the free additive (-9.39 ppm) a weak signal at -1.69 ppm appeared, that can be attributed to the formation of adduct between diphenyl phosphate (**A1**) and Shvo's complex (**C1**) (**Complex 1**). Interestingly, when to the mixture of Shvo's complex (**C1**) and diphenyl phosphate (**A1**) (1:1) the enamine 3-(4-methoxyphenylamino)-but-2-enoic acid ethyl ester (**3''aa**) was added (obtained separately by synthetic procedures), the signal was shifted to -0.31 ppm that could be explained by the formation of the corresponding adduct between **A1**, **C1** and **3''aa** (**Figure 4.5A-c**, **Complex 2**). Analogous interactions between metal complexes and Brønsted acid additives (as **Complex 2** in our case) were reported by Beller using Knölker's iron complex and chiral Brønsted acid (3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphtyl-2,2'-diyl hydrogen phosphate (*S*)-TRIP) for the hydrogenation of imines[39,47] and by Gandon using Vaska's complex with chiral phosphate additive for the enantioselective carbocyclization of 1,6-enynes.[48] Herein **Complex 2** is displayed as the more stable, amine-coordinated species, which

is proposed to form upon interaction of **3'aa** and **A1** with the 'reducing' half of Shvo's complex as depicted below.



In spectrum **Figure 4.5A-c**, the chemical shift at -11.64 ppm can be attributed to **Adduct 3**, between **A1** and **3'.** This has been additionally confirmed by separately recording the spectrum of readily prepared **3''** and **A1** without the catalyst, displaying a shift at -11.39 ppm (**Figure 4.5A-d**). Rueping observed a very similar chemical shift (singlet at approximately -13 ppm in ^{31}P NMR spectrum) related to the formation of intermolecular hydrogen bonded species between diphenyl phosphate and (*E*)-*N*-phenyl-1-(*p*-tolyl) methanimine, comparable to **Adduct 3** in our case.[49] It has to be noted, that we display here **Adduct 3** as a hydrogen bonded species. In their work Rueping detected the hydrogen bonded as well as the corresponding ionic species by low temperatures ^{1}H NMR, with only one ^{31}P NMR signal observed around -13 ppm.

We assume that in the absence of **A1**, tautomerization of the imine **3'aa** (formed during the borrowing hydrogen cycle) to the corresponding enamine **3''aa** would take place, while in the presence of **C1** and **A1, 3'aa** is rapidly reduced to the desired *β*-amino acid ester (**3**) *via* the ruthenium-amine complex (**Figure 4.5B**, **Complex 2**).

4.2.3 Scope of the methodology

Next, the scope and limitation of the newly established method were explored. A wide range of anilines were effectively coupled with ethyl 3-hydroxybutanoate (**Figure 4.6**). With anilines bearing electron-donating substituents (**2a-f**), including those with bulky groups (**2e**, **2f**), 48-87% isolated product yields were achieved. Anilines with electron-withdrawing substituents (**2g-l**) also showed generally high reactivity affording products **3ag-al** in 47-87% isolated yield. Functional groups such as $–NO_2$, –CN, $–CH_3COOCH_3$ were well-tolerated under the reaction conditions. Notably, also when **2p** and **2r** containing heterocycles were examined, the alkylated *β*-amino acid esters (**3ap**, **3ar**) were obtained in 78% and 44% isolated yield, respectively.

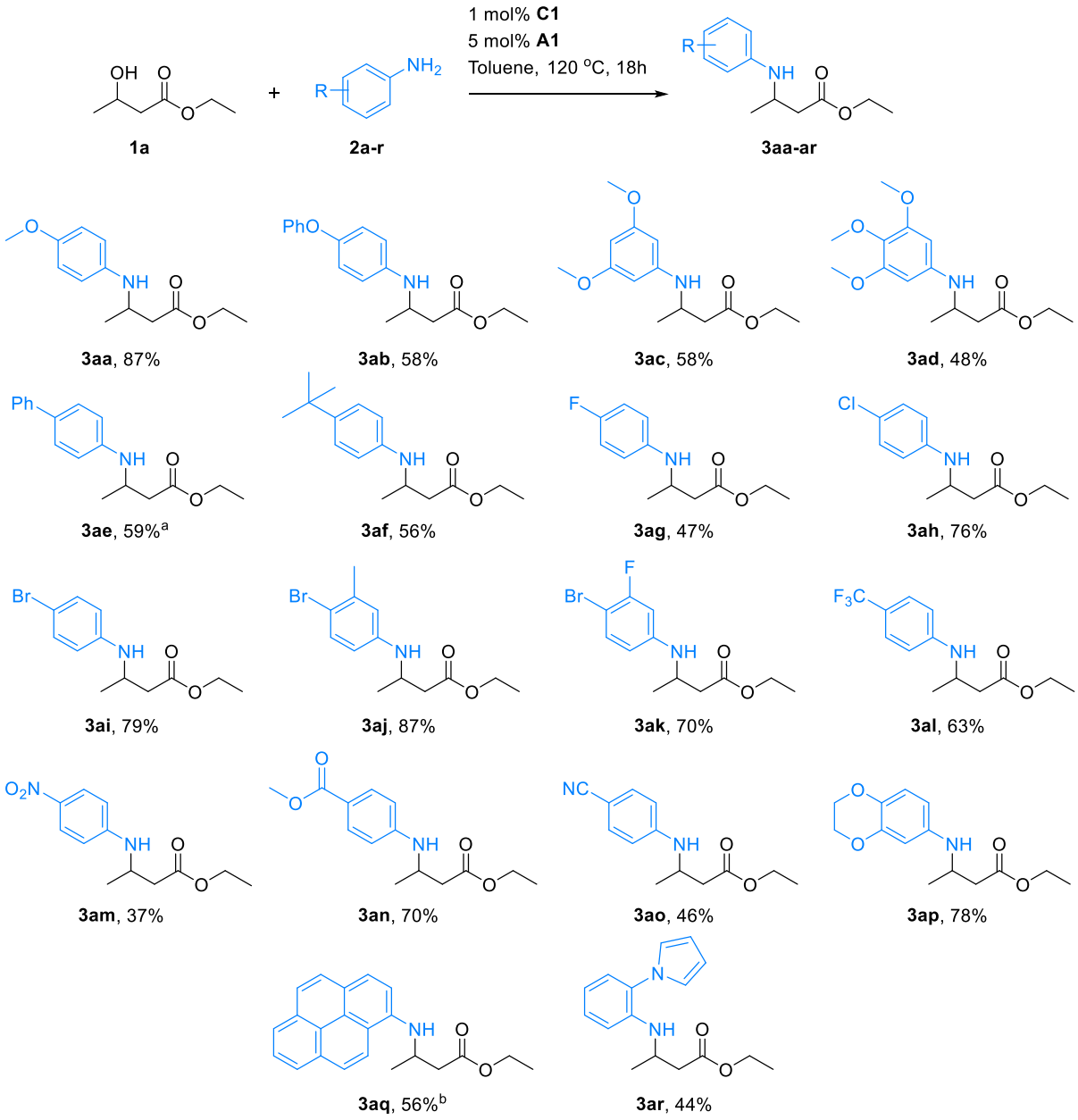


Figure 4.6: Direct catalytic amination of the *β*-hydroxyl acid ester **1a** with variation of the amine substrate. General reaction conditions: General Procedure, 1 mmol of **1a**, 0.5 mmol of **2a-r**, 1 mol% Shvo's complex (**C1**), 5 mol% additive (**A1**), 2 mL toluene, 18 hours, 120 °C, under argon, full conversion unless otherwise indicated, isolated yields are presented. [a] 95% conversion. [b] 94% conversion.

Furthermore, we examined different *β*-hydroxyl acid esters as coupling partners to *p*-anisidine (**2a**)/ *p*-bromoaniline (**2i**) (**Figure 4.7**). Employing *β*-hydroxyl acid esters with bulky aliphatic substituents at *β*-position (**1b**, **1c**) delivered the desired *β*-amino acid esters (**3ba**, **3bi, 3ca** and **3ci**) in good yields (79%, 68%, 78% and 54%, respectively) while with ethyl 3-hydroxy-3-phenylpropanoate (**1d**) generally lower isolated yields were obtained (**3da-3di**, 43-48%). Excellent results (81-96%) were obtained with ethyl 3-hydroxy-2,2-dimethylpropanoate (**1e**) comprising two methyl substituents in the *α*-position (**3ea-3ei**, 81-96%). In comparison, **1f** bearing an *α*-phenyl substituent displayed moderate results (**3fa-3fi**, 33-59%).

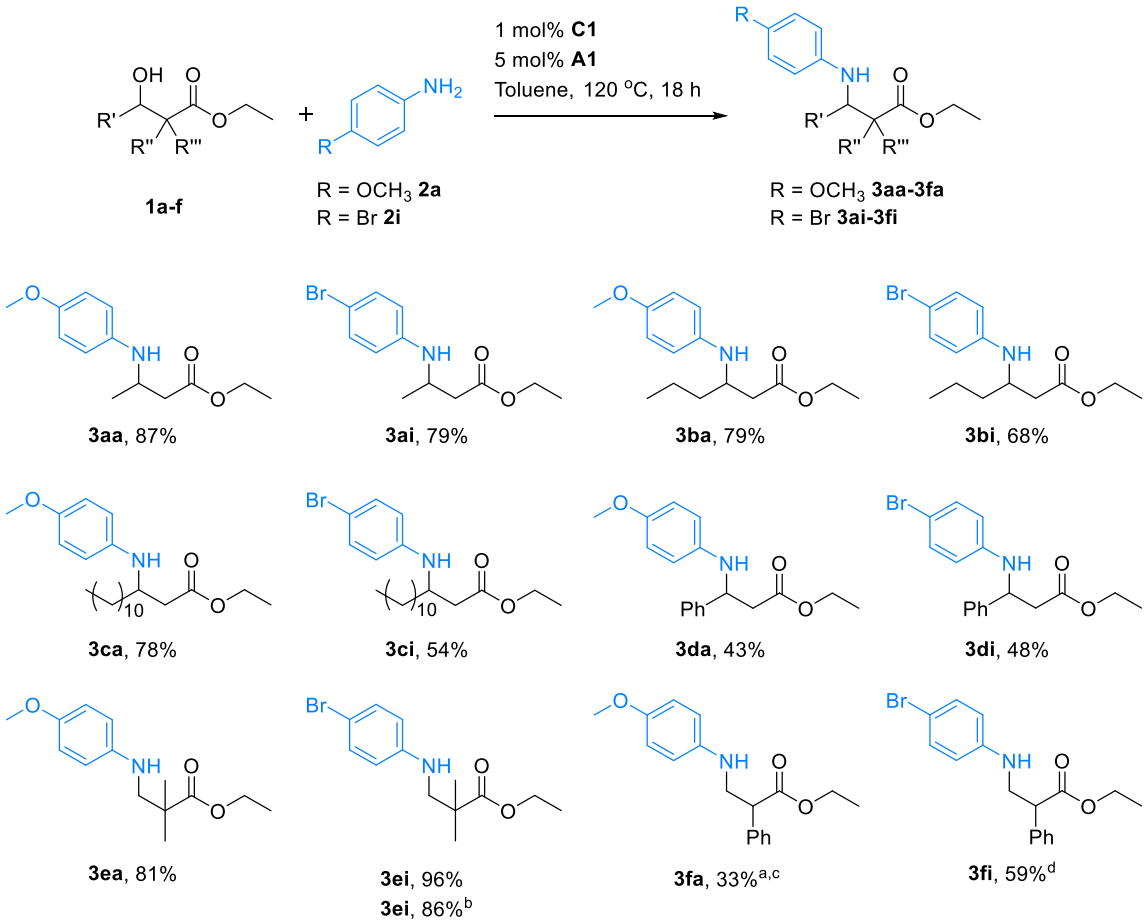


Figure 4.7: Direct catalytic amination of the *β*-hydroxyl acid esters using aniline derivatives **2a** and **2i** with variation of the *β*-hydroxyl acid ester substrate. General reaction conditions: General Procedure, 1 mmol of **1a-f**, 0.5 mmol of **2a** or **2i,** 1 mol% Shvo's complex (**C1**), 5 mol% additive (**A1**), 2 mL toluene, 18 hours, 120 °C, under argon, full conversion unless otherwise indicated, isolated yields are presented. [a] 48 h. [b] 12 mmol of **1e**, 6 mmol of **2i,** 1 mol% Shvo's complex (**C1**), 5 mol% additive (**A1**), 5 mL toluene, 18 hours, 120 °C, under argon. [c] 79% conversion. [d] 83% conversion.

Having a highly selective method in hand for obtaining **3ei**, the power of our developed catalytic method was demonstrated in the two-step, gram-scale synthesis of a *β*-lactam (**4ei, Figure 4.8**). A 12-fold upscale of the amination of **1e** with *p*-bromoaniline **2i** (**Figure 4.7**) furnished the desired *β*-amino acid ester (**3ei**) with excellent isolated yield (86%), which was subsequently cyclized following a known literature procedure (**Figure 4.8**).[50]

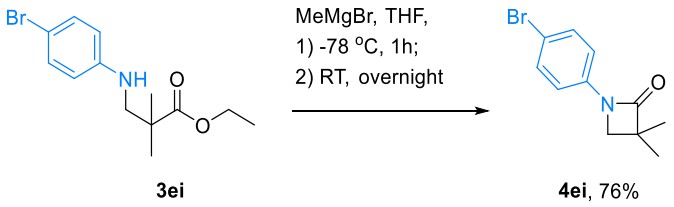


Figure 4.8: Gram-scale synthesis of *β*-amino acid ester (**3ei**) and the application of the developed method in the synthesis of a *β*-lactam.

4.2.4 Bio-based *β*-amino acid esters from 3-hydroxypropionates

Finally, to demonstrate the feasibility of this method for obtaining renewable *β*-amino acid esters in a remarkably simple manner, we turned our attention to the direct catalytic amination of esters of bio-based 3-HP, identified as one of the Top 12 value-added platform chemicals.[14,16] It is important to mention that the ethyl ester of 3-HP can be directly obtained from renewable resources, similarly to the acid 3-HP itself.[18,19] Herein we have investigated the use of commercially available *tert*-butyl 3-hydroxypropionate (**1i**) as well as ethyl 3-hydroxypropanoate (**1j**) as substrates. Gratifyingly, both **1i** as well as **1j** were smoothly aminated with **2a-o** using the methodology developed herein (**Figure 4.9**). Notably, the conversion was significantly decreased in the absence of additive **A1** (50%), confirming the necessity of the catalytic system designed above. Interestingly, selective double *N*-alkylation of **2a** with **1i-j** was easily achieved by doubling the catalyst amount to 2 mol%, showing modularity of the method. The isolated yields of products obtained from the 3-HP esters, were somewhat lower compared to previously tested substrates (especially 3-hydroxy-2,2-dimethylpropanoate (**1e**)), thus the possibility of side reactions cannot be ruled out, although no side products (e.g. amides) were detectable by GC-MS or GC-FID methods. Hydrolysis of the 3-HP esters or the product *β*-amino acid esters to the corresponding carboxylic acids would be a possible pathway. Interestingly, with substrate **1e,** minimal amount of side products attributable to intermolecular transesterification processes were seen. Similar reactivity may also be expected starting from the bio-based 3-HP esters **1i** or **1j** albeit presumably toward higher molecular weight analogues due to the decreased steric hindrance of the primary alcohol moiety.

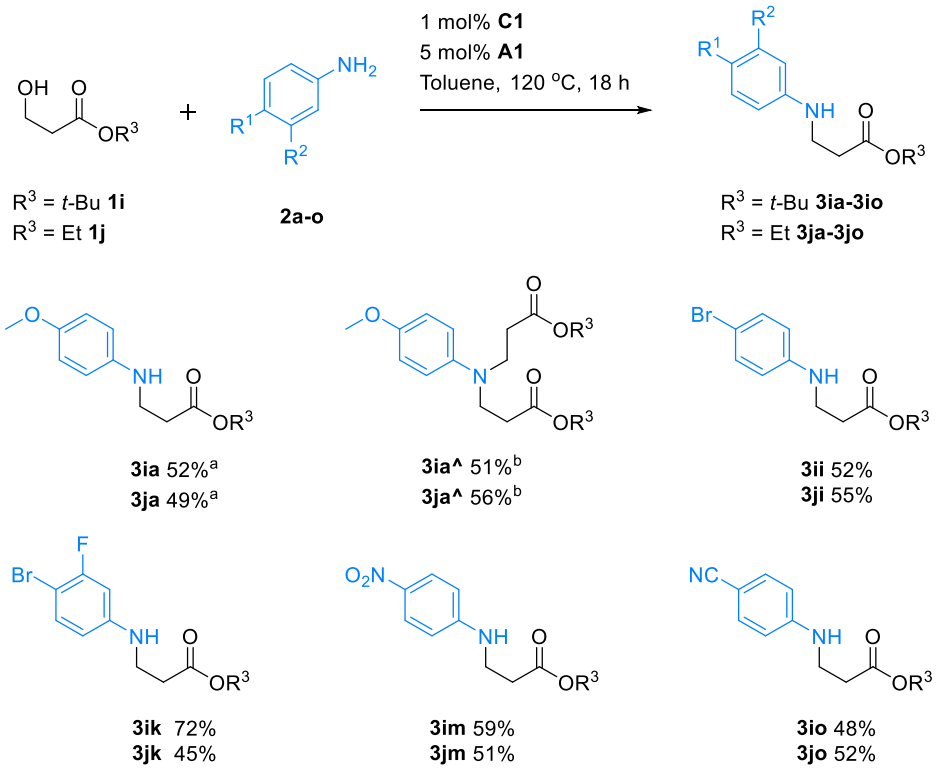


Figure 4.9: Novel route to bio-based *β*-amino acid esters *via* direct catalytic amination of *tert*-butyl 3-hydroxypropionate. General reaction conditions: General Procedure, 1 mmol of **1i-j**,

0.5 mmol of **2a-o,** 1 mol% Shvo's complex (**C1**), 5 mol% additive (**A1**), 2 mL toluene, 18 hours, 120 °C, under argon, isolated yields are presented. [a] 48 h. [b] 1 mmol of **1i-j**, 0.5 mmol of **2a,** 2 mol% Shvo's complex (**C1**), 5 mol% additive (**A1**), 2 mL toluene, 48 hours, 120 °C, under argon.

4.3 Conclusion

In summary, we have achieved the first direct catalytic coupling of *β*-hydroxyl acid esters with amines to construct *β*-amino acid esters by cooperative catalysis using the combination of Shvo's catalyst and the Brønsted acid additive – diphenyl phosphate. The methodology is highly atom-economic, demonstrates a broad scope, excellent functional-group tolerance and potential application for the synthesis of *β*-lactams. Notably, the method allows for catalytic amination of a commercially available ester of 3-hydroxypropionic acid, an important bio-based platform chemical, opening an entirely new possibility to access valuable *β*-amino acid scaffolds from several classes of abundant renewable resources. The obtained *β*-amino acid esters can be applied as value-added building blocks or further transformed to a variety of bio-based amines, diamines, amino-alcohols usable in the fine chemical, materials or polymer chemistry sectors. The presented novel cooperative catalytic system should be broadly applied, in the future, for the waste-free amination of other highly oxygenated renewable building blocks.

4.4 Experimental section

4.4.1 General methods

All reactions were carried out under an argon atmosphere using oven (120 °C) dried glassware and using standard Schlenk techniques. 1-Hydroxytetraphenylcyclopentadienyl-(tetraphenyl-2,4-cyclopentadien-1-one)-μ-hydrotetracarbonyldiruthenium(II) (Shvo's catalyst, **C1**) was purchased from Strem Chemicals, Inc. 3-(4-Methoxyphenylamino)-but-2-enoic acid ethyl ester (**3''aa**) was synthesized according to the literature procedure.[46] All other reagents were purchased from Sigma-Aldrich, Acros and TCI in reagent or higher grade and were used as received without further purification.

Chromatography and spectroscopy

Column chromatography was performed using Merck silica gel type 9385 230-400 mesh and typically pentane and ethyl acetate as eluent.

Thin layer chromatography (TLC): Merck silica gel 60, 0.25 mm. The components were visualized by UV or $KMnO_4$ staining.

Gas Chromatography (GC) was used for product identification as well as determination of conversion and selectivity values. Product identification was performed by GC-MS (Shimadzu QP2010 Ultra) with an HP-1MS column, and helium as carrier gas. GC-MS method: The

temperature program started at 50 °C for 5 min, heated by 30°C/minute to 250 °C and held for 15 min.

Conversions and product selectivities were determined by GC-FID (Agilent Technologies 6890) with an HP-5MS column using nitrogen as carrier gas. GC-FID analysis method: The temperature program started at 50 °C for 5 min, heated by 30°C/min to 320 °C and held for 15 min.

Mass spectrometry: Mass spectra were recorded on an AEI-MS-902 mass spectrometer (EI^+) or an LTQ Orbitrap XL (ESI^+).

NMR spectroscopy: ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 400, Agilent MR 400 (400 and 101 MHz, respectively), Varian Inova 500 (500 and 126 MHz, respectively) and Bruker Avance NEO 600 (600 and 151 MHz, respectively) using $CDCl_3$ as a solvent. ^1H and ^{13}C NMR spectra were recorded at room temperature. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 for ^1H, 77.00 for ^{13}C; Toluene-d_8: 7.09, 7.01, 6.97, 2.08 for ^1H, 137.48, 128.87, 127.96, 125.13, 20.43 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br. = broad, m = multiplet), coupling constants (Hz), and integration.

4.4.2 Representative procedures

General procedure for the preparation of *β*-hydroxyl acid esters

Thionyl chloride (0.022 mol) was added dropwise to a stirred solution of the appropriate *β*-hydroxyl acid (0.02 mol) in dry EtOH (40 mL) at –30 °C at a rate such that the temperature of the reaction mixture did not rise above –30 °C. When the addition was complete, the solution was stirred at –30 °C for a further 10 min, and then left at room temperature for 4 h. Afterwards, the contents of the flask were poured into a mixture of finely crushed ice (75 g), a saturated aqueous Na_2CO_3 solution (20 mL), and Et_2O (50 mL). The prepared mixture was vigorously shaken in a separating funnel, and the organic layer was washed with brine and dried with anhydrous $MgSO_4$. After removal of the drying agent and evaporation of the solvent *in vacuo*, the resulting crude methyl ester *rac*-**1a-g** was purified by flash column chromatography to provide the pure *β*-hydroxyl acid ester.[51]

General procedure for the preparation of *β*-amino acid esters

An oven-dried 20 mL Schlenk tube, equipped with a stirring bar, was charged with amine (0.5 mmol, 1 equiv.), *β*-hydroxyl acid ester (1 mmol, 2 equiv.), Shvo's catalyst (0.005 mmol, 1 mol%), diphenyl phosphate (0.025 mmol, 5 mol%) and toluene (as a solvent, 2 mL). Solid materials were weighed into the Schlenk tube under air. Then the Schlenk tube was subsequently connected to an argon line and vacuum-argon exchange was performed three times. Liquid starting materials and solvent were charged under an argon stream. The Schlenk tube was capped and the mixture was rapidly stirred at room temperature for 1 min, then was placed into a pre-heated oil bath at 120 °C and stirred for a given time (typically, 18 h). Then,

the reaction mixture was cooled down to room temperature. After taking a sample (app. 0.5 mL) for GC analysis, the crude mixture was filtered through silica gel, eluted with ethyl acetate, and concentrated *in vacuo*. The residue was purified by flash column chromatography to provide the pure *β*-amino acid ester product.

Procedure for *in situ* ^{31}P NMR study

An oven-dried 20 mL Schlenk tube, equipped with a stirring bar, was charged (depending on the experiment) with Shvo's catalyst (0.02 mmol, 1 equiv.), diphenyl phosphate (0.02 mmol, 1 equiv.) and/or 3-(4-methoxyphenylamino)-but-2-enoic acid ethyl ester (**3''aa**, 0.02 mmol, 1 equiv.) and toluene-d_8 (as a solvent, 1 mL). Solid materials were weighed into the Schlenk tube under air. Then the Schlenk tube was subsequently connected to an argon line and vacuum-argon exchange was performed three times. Liquid starting materials and solvent were charged under an argon stream. The Schlenk tube was capped and the mixture was rapidly stirred at room temperature for 1 min, then was placed into a pre-heated oil bath (60 °C) and stirred for 15 min. Then, the reaction mixture was cooled down to room temperature. Preparing the sample, 0.6 mL of the reaction mixture was placed to a *J*-Young NMR tube under argon. All spectra were recorded using Bruker Avance NEO 600 machine.

Procedure for the hydrogenation of *N*-aryl enamine (3''aa)

An oven-dried 20 mL Schlenk tube, equipped with a stirring bar, was charged with Shvo's catalyst (0.002 mmol, 1 equiv.), diphenyl phosphate (0.01 mmol, 1 equiv.) or 3-(4-methoxyphenylamino)-but-2-enoic acid ethyl ester (**3''aa**, 0.2 mmol, 1 equiv.) and toluene (as a solvent, 2 mL). Solid materials were weighed into the Schlenk tube under air. Then the Schlenk tube was subsequently connected to an argon line and vacuum-argon exchange was performed three times. Liquid starting materials and solvent were charged under an argon stream. The Schlenk tube was capped and the mixture was rapidly stirred at room temperature for 1 min. At the same time the pre-dried autoclave, equipped with the stirring bar, was purged three times with hydrogen. Under the steam of hydrogen, the reaction mixture was transferred from the Schlenk tube to the autoclave and heated at 90 °C for the 15 min. The autoclave was then cooled to RT and the reaction mixture was transferred to a flask. The reaction mixture was analysed by GS-MS and GC-FID to determine conversion of the reaction.

Deuterium incorporation experiment using 1b-d1 as a substrate

An oven-dried 20 mL Schlenk tube, equipped with a stirring bar, was charged with Shvo's catalyst (0.001 mmol, 1 mol%), diphenyl phosphate (0.005 mmol, 5 mol%), ethyl 3-hydroxyhexanoate-3-d (**1b-d1**, 0.1 mmol, 1 equiv.), *p*-anisidine (**2a**, 0.1 mmol, 1 equiv.) and toluene-d_8 (as a solvent, 0.6 mL). Solid materials were weighed into the Schlenk tube under air. Then the Schlenk tube was subsequently connected to an argon line and vacuum-argon exchange was performed three times. Liquid starting materials and solvent were charged under an argon stream. The Schlenk tube was capped and the mixture was rapidly stirred at room temperature for 1 min, then was placed into a pre-heated oil bath (120 °C) and stirred for 18 h. Then, the reaction mixture was cooled down to room temperature. Preparing the sample, 0.6

mL of the reaction mixture was placed to a *J*-Young NMR tube under argon. All spectra were recorded using Varian Mercury Plus 400 machine.

Deuterium incorporation experiment using benzyl alcohol-*α,α*-d_2 as a substrate

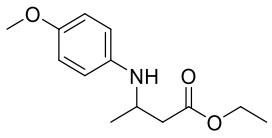
An oven-dried 20 mL Schlenk tube, equipped with a stirring bar, was charged with Shvo's catalyst (0.001 mmol, 1 mol%), diphenyl phosphate (0.005 mmol, 5 mol%), benzyl alcohol-*α,α*-d_2 (0.1 mmol, 1 equiv.), aniline (0.1 mmol, 1 equiv.) and toluene-d_8 (as a solvent, 0.6 mL). Solid materials were weighed into the Schlenk tube under air. The Schlenk tube was subsequently connected to an argon line and vacuum-argon exchange was performed three times. Liquid starting materials and solvent were charged under an argon stream. The Schlenk tube was capped and the mixture was rapidly stirred at room temperature for 1 min, then was placed into a pre-heated oil bath (120 °C) and stirred for 18 h. Then, the reaction mixture was cooled down to room temperature. Preparing the sample, 0.6 mL of the reaction mixture was placed to a *J*-Young NMR tube under argon. All spectra were recorded using Bruker Avance NEO 600 machine.

Procedure for amination of chiral *β*-hydroxyl acid esters

An oven-dried 20 mL Schlenk tube, equipped with a stirring bar, was charged with *p*-anisidine (**2a**, 0.5 mmol, 1 equiv.), ethyl (*3R*)-3-hydroxybutanoate (**(*R*)-1a**) or ethyl (*3S*)-3-hydroxybutanoate (**(*S*)-1a**) (1 mmol, 2 equiv.), Shvo's catalyst (0.005 mmol, 1 mol%), diphenyl phosphate (0.025 mmol, 5 mol%) and toluene (as a solvent, 2 mL). Solid materials were weighed into the Schlenk tube under air. Then the Schlenk tube was subsequently connected to an argon line and vacuum-argon exchange was performed three times. Liquid starting materials and solvent were charged under an argon stream. The Schlenk tube was capped and the mixture was rapidly stirred at room temperature for 1 min, then was placed into a pre-heated oil bath at 120 °C and stirred for 18 h. Then, the reaction mixture was cooled down to room temperature; the reaction mixture was analysed by GS-MS and GC-FID to determine conversion and selectivity of the reaction. Enantiomeric excess was determined by chiral HPLC. Conditions: Chiralpak AD-H column, 90:10 heptane:isopropanol, 0.5 mL/min.

4.4.3 Spectral data of isolated compounds

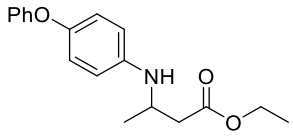
Ethyl 3-((4-methoxyphenyl)amino)butanoate (3aa)



The compound was synthesized according to the **General procedure** using 4-methoxyaniline (61.5 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to afford **3aa** (103 mg, 87% yield). Yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 90:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.77 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 8.8 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.84 (sext, *J* = 5.6 Hz, 1H), 3.73 (s, 3H, OCH_3), 3.35 (*br* s, 1H), 2.59 (dd,

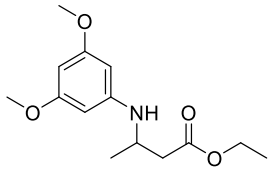
J = 14.8 Hz, *J* = 5.6 Hz, 1H), 2.38 (dd, *J* = 14.8 Hz, *J* = 6.8 Hz, 1H), 1.26-1.23 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.58, 155.04, 143.63, 118.09, 117.58, 63.05, 58.36, 49.89, 43.65, 23.27, 16.87. **HRMS** ($APCI^+$, m/z) calculated for $C_{13}H_{20}NO_3$ $[M+H]^+$: 238.14432; found: 238.14403. The spectral data are identical to the previously reported.[52]

Ethyl 3-((4-phenoxyphenyl)amino)butanoate (3ab)



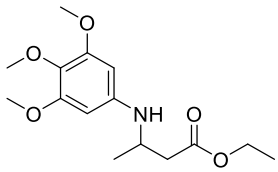
The compound was synthesized according to the **General procedure** using 4-phenoxyaniline (93 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to afford **3ab** (87 mg, 58% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 2H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.96-6.90 (m, 4H), 6.64 (d, *J* = 8.8 Hz, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.92 (sext, *J* = 6.0 Hz, 1H), 3.68 (*br* s, 1H), 2.64 (dd, *J* = 15.2 Hz, *J* = 5.6 Hz, 1H), 2.45 (dd, *J* = 15.2 Hz, *J* = 6.8 Hz, 1H), 1.30-1.25 (m, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.48, 161.65, 150.58, 146.08, 132.16, 124.65, 123.90, 119.84, 117.46, 63.16, 49.37, 43.67, 23.29, 16.91. **HRMS** ($APCI^+$, m/z) calculated for $C_{18}H_{22}NO_3$ $[M+H]^+$: 300.15997; found: 300.16013.

Ethyl 3-((3,5-dimethoxyphenyl)amino)butanoate (3ac)



The compound was synthesized according to the **General procedure** using 3,5-dimethoxyaniline (76.5 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to afford **3ac** (78 mg, 58% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 90:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.88-5.87 (m, 1H), 5.82-5.80 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.89 (sext, *J* = 5.6 Hz, 2H), 3.73 (s, 6H), 2.62 (dd, *J* = 14.8 Hz, *J* = 5.2 Hz, 1H), 2.41 (dd, *J* = 15.2 Hz, *J* = 6.8 Hz, 1H), 1.26-1.23 (m, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.40, 164.42, 151.39, 94.95, 92.63, 63.11, 57.76, 48.65, 43.61, 23.19, 16.86. **HRMS** ($APCI^+$, m/z) calculated for $C_{14}H_{22}NO_4$ $[M+H]^+$: 268.15488; found: 268.15501.

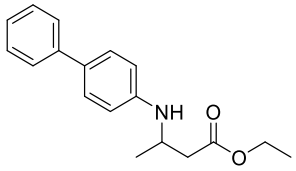
Ethyl 3-((3,4,5-trimethoxyphenyl)amino)butanoate (3ad)



The compound was synthesized according to the **General procedure** using 3,4,5-trimethoxyaniline (91.5 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to

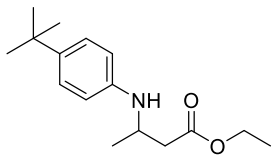
afford **3ad** (72 mg, 48% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 90:10 to 80:20). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.85 (s, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.90-3.81 (m, 1H), 3.79 (s, 6H), 3.73 (s, 3H), 2.60 (dd, *J* = 14.8 Hz, *J* = 5.2 Hz, 1H), 2.39 (dd, *J* = 14.8 Hz, *J* = 6.8 Hz, 1H), 1.26-1.21 (m, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.51, 156.62, 146.21, 132.89, 93.95, 63.67, 63.13, 58.56, 49.27, 43.74, 23.31, 16.85. **HRMS** (APCI$^+$, m/z) calculated for $C_{15}H_{24}NO_5$ $[M+H]^+$: 298.16545; found: 298.16533.

Ethyl 3-([1,1'-biphenyl]-4-ylamino)butanoate (3ae)



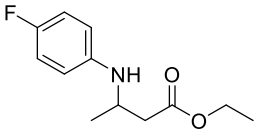
The compound was synthesized according to the **General procedure** using 4-aminobiphenyl (84.5 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to afford **3ae** (83 mg, 59% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.31-7.27 (m, 1H), 6.73 (d, *J* = 8.8 Hz, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.03 (sext, *J* = 6.0 Hz, 1H), 3.93 (*br* s, 1H), 2.68 (dd, *J* = 14.8 Hz, *J* = 5.2 Hz, 1H), 2.48 (dd, *J* = 14.8 Hz, *J* = 6.8 Hz, 1H), 1.34 (d, *J* = 6.4 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.47, 148.97, 143.86, 133.18, 131.34, 130.70, 128.96, 128.77, 116.48, 63.21, 48.75, 43.73, 23.33, 16.93. **HRMS** (APCI$^+$, m/z) calculated for $C_{18}H_{22}NO_2[M+H]^+$: 284.16505; found: 284.16462.

Ethyl 3-((4-(*tert*-butyl)phenyl)amino)butanoate (3af)



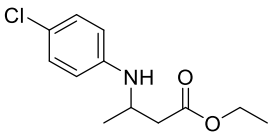
The compound was synthesized according to the **General procedure** using 4-(*tert*-butyl)aniline (74.5 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to afford **3af** (74 mg, 56% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 8.8 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.94 (sext, *J* = 6.0 Hz, 1H), 3.69 (*br* s, 1H), 2.65 (dd, *J* = 14.8 Hz, *J* = 5.2 Hz, 1H), 2.41 (dd, *J* = 14.8 Hz, *J* = 7.2 Hz, 1H), 1.30-1.25 (m, 15H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.56, 147.07, 143.05, 128.75, 115.98, 63.08, 48.90, 43.86, 36.51, 34.21, 23.42, 16.90. **HRMS** (APCI$^+$, m/z) calculated for $C_{16}H_{26}NO_2$ $[M+H]^+$: 264.19635; found: 264.19620.

Ethyl 3-((4-fluorophenyl)amino)butanoate (3ag)



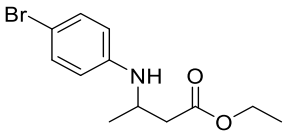
The compound was synthesized according to the **General procedure** using 4-fluoroaniline (56 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to afford **3ag** (53 mg, 47% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.90-6.85 (m, 2H), 6.56 (dd, *J* = 9.2 Hz, *J* = 4.8 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.85 (sext, *J* = 6.0 Hz, 1H), 3.61 (*br* s, 1H), 2.58 (dd, *J* = 14.8 Hz, *J* = 5.2 Hz, 1H), 2.41 (dd, *J* = 14.8 Hz, *J* = 6.4 Hz, 1H), 1.26-1.23 (m, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.43, 158.59 (d, J_{CF} = 236.3 Hz), 145.83, 118.38 (d, J_{CF} = 22.2 Hz), 117.36 (d, J_{CF} = 7.1 Hz), 63.14, 49.53, 43.55, 23.18, 16.85. **HRMS** (APCI$^+$, m/z) calculated for $C_{12}H_{17}FNO_2$ $[M+H]^+$: 226.12433; found: 226.12396. The spectral data are identical to the previously reported.[53]

Ethyl 3-((4-chlorophenyl)amino)butanoate (3ah)



The compound was synthesized according to the **General procedure** using 4-chloroaniline (64 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to afford **3ah** (92 mg, 76% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 8.8 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.88 (sext, *J* = 6.0 Hz, 1H), 3.81 (*br* s, 1H), 2.58 (dd, *J* = 15.2 Hz, *J* = 5.6 Hz, 1H), 2.42 (dd, *J* = 14.8 Hz, *J* = 6.4 Hz, 1H), 1.26-1.23 (m, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.31, 148.08, 131.79, 124.77, 117.31, 63.20, 48.87, 43.48, 23.11, 16.86. **HRMS** (APCI$^+$, m/z) calculated for $C_{12}H_{17}ClNO_2[M+H]^+$: 242.09478; found: 242.09475. The spectral data are identical to the previously reported.[54]

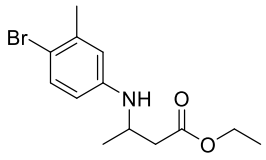
Ethyl 3-((4-bromophenyl)amino)butanoate (3ai)



The compound was synthesized according to the **General procedure** using 4-bromoaniline (86 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to afford **3ai** (112 mg, 79% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 8.8 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.88 (sext, *J* = 6.0 Hz, 1H), 2.57 (dd, *J* = 14.8 Hz, *J* = 5.6 Hz, 1H), 2.43 (dd, *J* = 14.8 Hz, *J* = 6.4 Hz, 1H), 1.26-1.23 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.29, 148.52, 134.67, 117.76, 111.76, 63.21, 48.75, 43.46, 23.10, 16.87. **HRMS** (APCI$^+$, m/z)

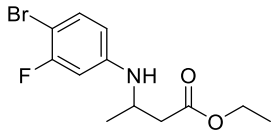
calculated for $C_{12}H_{17}BrNO_2[M+H]^+$: 286.04427; found: 286.04430. The spectral data are identical to the previously reported.[52]

Ethyl 3-((4-bromo-3-methylphenyl)amino)butanoate (3aj)



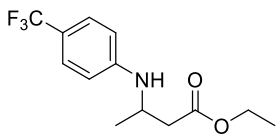
The compound was synthesized according to the **General procedure** using 4-bromo-3-methylaniline (93 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to afford **3aj** (130 mg, 87% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.8 Hz, 1H), 6.50 (d, *J* = 2.8 Hz, 1H), 6.34 (dd, *J* = 8.8 Hz, *J* = 2.8 Hz, 1H), 4.14 (q, *J* = 6.8 Hz, 2H), 3.88 (sext, *J* = 6.0 Hz, 1H), 3.78 (*br* s, 1H), 2.58 (dd, *J* = 15.2 Hz, *J* = 5.2 Hz, 1H), 2.42 (dd, *J* = 14.8 Hz, *J* = 6.4 Hz, 1H), 2.30 (s, 3H), 1.27-1.23 (m, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.34, 148.82, 140.98, 135.38, 118.60, 115.33, 114.56, 63.18, 48.75, 43.53, 25.72, 23.15, 16.88. **HRMS** ($APCI^+$, m/z) calculated for $C_{13}H_{19}BrNO_2$ $[M+H]^+$: 300.05992; found: 300.06026.

Ethyl 3-((4-bromo-3-fluorophenyl)amino)butanoate (3ak)



The compound was synthesized according to the **General procedure** using 4-bromo-3-fluoroaniline (95 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to afford **3ak** (107 mg, 70% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.22 (t, *J* = 8.0 Hz, 1H), 6.37 (dd, *J* = 11.2 Hz, *J* = 2.8 Hz, 1H), 6.27 (dd, *J* = 8.4 Hz, *J* = 2.4 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.05 (*br* s, 1H), 3.84 (sext, *J* = 6.4 Hz, 1H), 2.56 (dd, *J* = 15.2 Hz, *J* = 5.2 Hz, 1H), 2.44 (dd, *J* = 15.2 Hz, *J* = 6.8 Hz, 1H), 1.26-1.22 (m, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.12, 162.49 (d, J_{CF} = 244.9 Hz), 150.56 (d, J_{CF} = 9.1 Hz), 136.04, 113.27 (d, J_{CF} = 2.5 Hz), 103.69 (d, J_{CF} = 26.2 Hz), 97.36 (d, J_{CF} = 21.6 Hz), 63.30, 48.72, 43.34, 22.96, 16.84. **HRMS** ($APCI^+$, m/z) calculated for $C_{12}H_{16}BrFNO_2$ $[M+H]^+$: 304.03484; found: 304.03449.

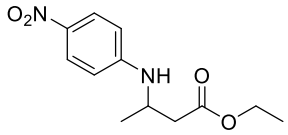
Ethyl 3-((4-(trifluoromethyl)phenyl)amino)butanoate (3al)



The compound was synthesized according to the **General procedure** using 4-(trifluoromethyl)aniline(81 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to afford **3ao** (86 mg, 63% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.4 Hz, 2H), 6.61 (d,

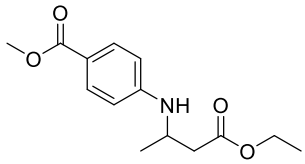
J = 8.8 Hz, 2H), 4.21 (*br* s, 1H, NH), 4.15 (q, *J* = 7.2 Hz, 2H), 3.97 (sext, *J* = 6.4 Hz, 1H), 2.60 (dd, *J* = 15.2 Hz, *J* = 5.2 Hz, 1H), 2.47 (dd, *J* = 15.2 Hz, *J* = 6.8 Hz, 1H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 171.51, 149.39, 126.68, 124. 94 (q, *J* = 716.4 Hz), 118.94 (q, *J* = 32.62 Hz), 112.40, 60.65, 45.64, 40.80, 20.39, 14.16. **HRMS** ($APCI^+$, m/z) calculated for $C_{13}H_{17}F_3NO_2$ $[M+H]^+$: 276.12114; found: 276.12100.

Ethyl 3-((4-nitrophenyl)amino)butanoate (3am)



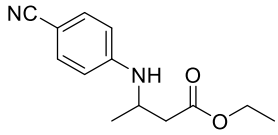
The compound was synthesized according to the **General procedure** using 4-nitroaniline (69 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to afford **3am** (47 mg, 37% yield). Bright yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 90:10 to 80:20). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 9.2 Hz, 2H), 6.54 (d, *J* = 9.6 Hz, 2H), 4.88 (*br* s, 1H, NH), 4.14 (q, *J* = 7.2 Hz, 2H), 4.03 (sext, *J* = 6.0 Hz, 1H), 2.60 (dd, *J* = 15.2 Hz, *J* = 5.2 Hz, 1H), 2.52 (dd, *J* = 15.2 Hz, *J* = 6.4 Hz, 1H), 1.32 (d, *J* = 6.4 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.87, 154.77, 140.64, 129.13, 114.09, 63.49, 48.30, 43.22, 22.90, 16.82. **HRMS** ($APCI^+$, m/z) calculated for $C_{12}H_{17}N_2O_4$ $[M+H]^+$: 253.11883; found: 253.11823.

Methyl 4-((4-ethoxy-4-oxobutan-2-yl)amino)benzoate (3an)



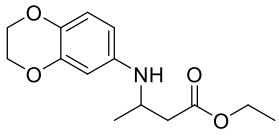
The compound was synthesized according to the **General procedure** using methyl 4-aminobenzoate (75.5 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to afford **3an** (93 mg, 70% yield). Colorless oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 90:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.8 Hz, 2H), 6.54 (d, *J* = 8.8 Hz, 2H), 4.40 (*br* s, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.01-3.97 (m, 1H), 3.82 (s, 3H), 2.59 (dd, *J* = 15.2 Hz, *J* = 5.2 Hz, 1H), 2.44 (dd, *J* = 14.8 Hz, *J* = 6.4 Hz, 1H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.22 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.10, 169.87, 153.32, 134.25, 121.08, 114.59, 63.28, 54.15, 48.11, 43.48, 23.06, 16.82. **HRMS** ($APCI^+$, m/z) calculated for $C_{14}H_{20}NO_4$ $[M+H]^+$: 266.13923; found: 266.13895.

Ethyl 3-((4-cyanophenyl)amino)butanoate (3ao)



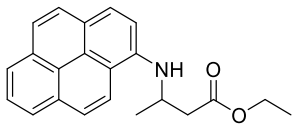
The compound was synthesized according to the **General procedure** using 4-aminobenzonitrile (59 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to afford **3al** (54 mg, 46% yield. Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 90:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 4.53 (*br* s, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.01-3.90 (m, 1H), 2.57 (dd, *J* = 15.2 Hz, *J* = 5.6 Hz, 1H), 2.46 (dd, *J* = 15.2 Hz, *J* = 6.8 Hz, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 170.30, 149.04, 132.79, 119.32, 111.64, 97.90, 59.75, 44.41, 39.66, 19.31, 13.17. **HRMS** (APCI$^+$, m/z) calculated for $C_{13}H_{17}N_2O_2$ $[M+H]^+$: 233.12900; found: 233.12848.

Ethyl 3-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)amino)butanoate (3ap)



The compound was synthesized according to the **General procedure** using 1,4-benzodioxan-6-amine (76 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to afford **3ap** (103 mg, 78% yield). Yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 95:5 to 90:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.67 (d, *J* = 8.8 Hz, 1H), 6.18-6.13 (m, 2H), 4.20-4.09 (m, 6H), 3.79 (sext, *J* = 6.0 Hz, 1H), 3.40 (*br* s, 1H), 2.57 (dd, *J* = 15.2 Hz, *J* = 5.2 Hz, 1H), 2.37 (dd, *J* = 14.8 Hz, *J* = 6.8 Hz, 1H), 1.25-1.20(m, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.47, 146.71, 144.39, 138.54, 120.31, 110.45, 105.36, 67.35, 66.81, 63.04, 49.58, 43.59, 23.20, 16.87. **HRMS** (APCI$^+$, m/z) calculated for $C_{14}H_{20}NO_4$ $[M+H]^+$: 266.13923; found: 266.13934.

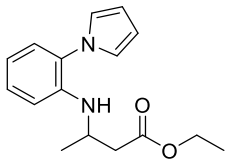
Ethyl 3-(pyren-1-ylamino)butanoate (3aq)



The compound was synthesized according to the **General procedure** using 1-aminopyrene (109.5 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to afford **3aq** (110 mg, 56% yield). Bright yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.09-7.81 (m, 8H), 7.42-7.40 (m, 1H), 5.17 (*br* s, 1H), 4.39-4.30 (m, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 2.82 (dd, *J* = 15.2 Hz, *J* = 5.2 Hz, 1H), 2.68 (dd, *J* = 15.2 Hz, *J* = 6.4 Hz, 1H), 1.49 (d, *J* = 6.4 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 3H).**^{13}C NMR** (151 MHz, $CDCl_3$): δ 172.02, 141.21, 132.44, 131.74, 127.75, 126.43, 126.24, 125.97,

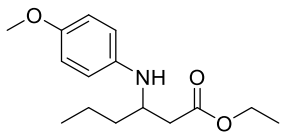
125.75, 123.93, 123.45, 123.34, 119.61, 117.17, 109.93, 60.74, 46.56, 40.99, 20.64, 14.32. **HRMS** (APCI$^+$, m/z) calculated for $C_{22}H_{22}NO_2[M+H]^+$: 332.16505; found: 332.16320.

Ethyl 3-((2-(1H-pyrrol-1-yl)phenyl)amino)butanoate (3ar)



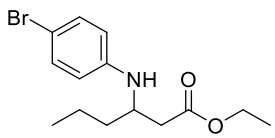
The compound was synthesized according to the **General procedure** using 2-(1H-pyrrol-1-yl)aniline (79 mg, 0.5 mmol) and ethyl 3-hydroxybutanoate (132 mg, 1 mmol) to afford **3ar** (60 mg, 44% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (td, *J* = 6.4 Hz, *J* = 1.6 Hz, 1H), 7.14 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 6.81 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H), 6.79-6.78 (m, 2H), 6.74 (td, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H), 6.36-6.35 (m, 2H), 4.12 (q, *J* = 6.8 Hz, 2H), 3.97 (sext, *J* = 6.4 Hz, 1H), 3.84 (*br* s, 1H), 2.57 (dd, *J* = 14.8 Hz, *J* = 5.6 Hz, 1H), 2.36 (dd, *J* = 14.8 Hz, *J* = 7.2 Hz, 1H), 1.25-1.20 (m, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.09, 145.08, 131.61, 130.29, 130.06, 124.51, 119.42, 114.61, 112.10, 63.19, 48.46, 43.89, 23.23, 16.86. **HRMS** (APCI$^+$, m/z) calculated for $C_{16}H_{21}N_2O_2$ $[M+H]^+$: 273.16030; found: 273.15992.

Ethyl 3-((4-methoxyphenyl)amino)hexanoate (3ba)



The compound was synthesized according to the **General procedure** using 4-methoxyaniline (61.5 mg, 0.5 mmol) and ethyl 3-hydroxyhexanoate (160 mg, 1 mmol) to afford **3ba** (104 mg, 79% yield). Yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 90:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.76 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 9.2 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 3H, OCH_3), 3.71 (p, *J* = 6.0 Hz, 1H), 2.51 (dd, *J* = 14.8 Hz, *J* = 5.6 Hz, 1H), 2.45 (dd, *J* = 14.8 Hz, *J* = 6.4 Hz, 1H), 1.56-1.34 (m, 4H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.76, 154.84, 144.10, 117.76, 117.58, 63.00, 58.39, 54.08, 41.95, 39.95, 22.01, 16.86, 16.65. **HRMS** (APCI$^+$, m/z) calculated for $C_{15}H_{24}NO_3$ $[M+H]^+$: 266.17562; found: 266.17539.

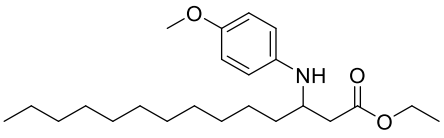
Ethyl 3-((4-bromophenyl)amino)hexanoate (3bi)



The compound was synthesized according to the **General procedure** using 4-bromoaniline (86 mg, 0.5 mmol) and ethyl 3-hydroxyhexanoate (160 mg, 1 mmol) to afford **3bi** (106 mg, 68% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc

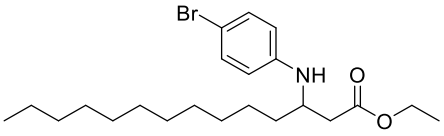
95:5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 8.8 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.77-3.72 (m, 2H), 2.54-2.44 (m, 2H), 1.57- 1.21 (m, 4H), 1.22 (t, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.46, 149.00, 134.64, 117.56, 111.45, 63.17, 52.96, 41.91, 39.88, 21.99, 16.85, 16.61. **HRMS** ($APCI^+$, m/z) calculated for $C_{14}H_{21}BrNO_2$ $[M+H]^+$: 314.07557; found: 314.07532.

Ethyl 3-((4-methoxyphenyl)amino)tetradecanoate (3ca)



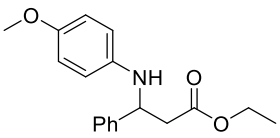
The compound was synthesized according to the **General procedure** using 4-methoxyaniline (61.5 mg, 0.5 mmol) and ethyl 3-hydroxytetradecanoate (272 mg, 1 mmol) to afford **3ca** (147 mg, 78% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 98:2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.77 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 9.2 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 3.69 (p, *J* = 6.4 Hz, 1H),3.47 (*br* s, NH, 1H), 2.52 (dd, *J* = 15.2 Hz, *J* = 5.6 Hz, 1H), 2.45 (dd, *J* =15.2 Hz, *J* = 6.0 Hz, 1H), 1.57- 1.22 (m, 23H), 0.88 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.76, 154.86, 144.07, 117.80, 117.58, 63.00, 58.39, 54.37, 41.92, 37.73, 34.57, 32.29, 32.27, 32.23, 32.21, 32.19, 32.00, 28.80, 25.34, 16.86, 16.77. **HRMS** ($APCI^+$, m/z) calculated for $C_{23}H_{40}NO_3[M+H]^+$: 378.30082; found: 378.30132.

Ethyl 3-((4-bromophenyl)amino)tetradecanoate (3ci)



The compound was synthesized according to the **General procedure** using 4-bromoaniline (86 mg, 0.5 mmol) and ethyl 3-hydroxytetradecanoate (272 mg, 1 mmol) to afford **3ci** (116 mg, 54% yield). Light white oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 98:2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 9.2 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.80-3.70 (m, 2H), 2.54-2.44 (m, 2H), 1.56- 1.21 (m, 23H), 0.88 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 174.46, 148.96, 134.64, 117.58, 111.49, 63.15, 53.24, 41.87, 37.66, 34.57, 32.28, 32.27, 32.21, 32.16, 32.14, 31.99, 28.75, 25.34, 16.85, 16.78. **HRMS** ($APCI^+$, m/z) calculated for $C_{22}H_{37}BrNO_2[M+H]^+$: 426.20077; found: 426.20103.

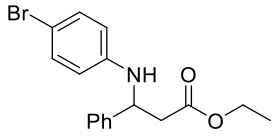
Ethyl 3-((4-methoxyphenyl)amino)-3-phenylpropanoate (3da)



The compound was synthesized according to the **General procedure** using 4-methoxyaniline (61.5 mg, 0.5 mmol) and ethyl 3-hydroxy-3-phenylpropanoate (194 mg, 1 mmol) to afford **3da**

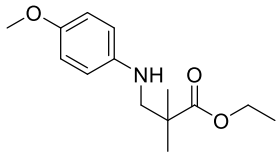
(84 mg, 48% yield). Yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 95:5 to 90:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38-7.22 (m, 5H), 6.70 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 8.8 Hz, 2H), 4.78-4.74 (m, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.70 (s, 3H), 2.79 (d, *J* = 6.8 Hz, 2H), 1.20 (t, *J* = 7.2 Hz, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.89, 154.95, 145.10, 143.66, 131.36, 130.02, 128.97, 117.81, 117.40, 63.38, 58.61, 58.34, 45.60, 16.80. **HRMS** ($APCI^+$, m/z) calculated for $C_{18}H_{22}NO_3$ $[M+H]^+$: 300.15997; found: 300.15973. The spectral data are identical to the previously reported.[55]

Ethyl 3-((4-bromophenyl)amino)-3-phenylpropanoate (3di)



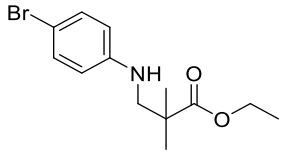
The compound was synthesized according to the **General procedure** using 4-bromoaniline (86 mg, 0.5 mmol) and ethyl 3-hydroxy-3-phenylpropanoate (194 mg, 1 mmol) to afford **3di** (65 mg, 43% yield). Yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 95:5 to 90:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.24 (m, 5H), 7.18 (d, *J* = 8.8 Hz, 2H), 6.44 (d, *J* = 8.8 Hz, 2H), 4.81-4.77 (m, 1H), 4.69 (*br* s, 1H), 4.12 (q, *J* = 6.8 Hz, 2H), 2.85-2.75 (m, 2H), 1.20 (t, *J* = 6.8 Hz, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.68, 148.48, 144.28, 134.50, 131.50, 130.26, 128.84, 117.94, 112.11, 63.53, 57.66, 45.44, 16.81. **HRMS** ($APCI^+$, m/z) calculated for $C_{17}H_{19}BrNO_2$ $[M+H]^+$: 348.05992; found: 348.05995.

Ethyl 3-((4-methoxyphenyl)amino)-2,2-dimethylpropanoate (3ea)



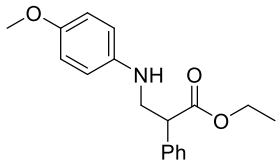
The compound was synthesized according to the **General procedure** using 4-methoxyaniline (61.5 mg, 0.5 mmol) and ethyl 3-hydroxy-2,2-dimethylpropanoate (146 mg, 1 mmol) to afford **3ea** (101 mg, 81% yield). Light orange oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 90:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.77 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 8.8 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 3H, OCH_3), 3.18 (s, 2H), 1.27 (s, 6H), 1.24 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 179.68, 154.72, 145.53, 117.49, 116.98, 63.29, 58.45, 56.64, 46.15, 26.21, 16.82. **HRMS** ($APCI^+$, m/z) calculated for $C_{14}H_{22}NO_3$$[M+H]^+$: 252.15997; found: 252.16005.

Ethyl 3-((4-bromophenyl)amino)-2,2-dimethylpropanoate (3ei)



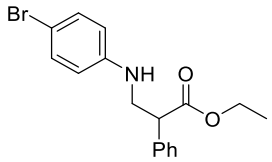
The compound was synthesized according to the **General procedure** using 4-bromoaniline (86 mg, 0.5 mmol) and ethyl 3-hydroxy-2,2-dimethylpropanoate (146 mg, 1 mmol) to afford **3ei** (143 mg, 96% yield). Colorless oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 95:5 to 90:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 8.8 Hz, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.04 (*br* s, 1H, NH), 3.18 (s, 2H), 1.24 (m, 9H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 179.50, 150.19, 134.47, 117.09, 111.29, 63.42, 55.20, 46.19, 26.15, 16.82. **HRMS** (APCI$^+$, m/z) calculated for $C_{13}H_{19}BrNO_2[M+H]^+$: 300.05992; found: 300.05953.

Ethyl 3-((4-methoxyphenyl)amino)-2-phenylpropanoate (3fa)



The compound was synthesized according to the **General procedure** using 4-methoxyaniline (61.5 mg, 0.5 mmol) and ethyl 3-hydroxy-2-phenylpropanoate (194 mg, 1mmol) to afford **3fa** (49 mg, 33% yield). Yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 90:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38-7.28 (m, 5H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.58 (d, *J* = 8.8 Hz, 2H), 4.21-4.08 (m, 2H), 3.93-3.89 (m, 1H), 3.82-3.75 (m, 4H), 3.42 (dd, *J* = 13.2 Hz, *J* = 6.4 Hz, 1H), 1.20 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 175.55, 155.06, 144.09, 139.57, 131.52, 130.69, 130.28, 117.62, 117.29, 63.64, 58.44, 53.59, 50.62, 16.74. **HRMS** (APCI$^+$, m/z) calculated for $C_{18}H_{22}NO_3$ $[M+H]^+$: 300.15997; found: 300.16017. The spectral data are identical to the previously reported.[56]

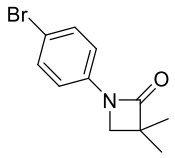
Ethyl 3-((4-bromophenyl)amino)-2-phenylpropanoate (3fi)



The compound was synthesized according to the **General procedure** using 4-bromoaniline (86 mg, 0.5 mmol) and ethyl 3-hydroxy-2-phenylpropanoate (194 mg, 1mmol) to afford **3fi** (103 mg, 59% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38-7.24 (m,7H), 6.48 (d, *J* = 8.8 Hz, 2H), 4.20-4.10 (m, 2H), 3.91-3.87 (m, 1H), 3.82-3.77 (m, 1H), 3.43 (dd, *J* = 13.6 Hz, *J* = 6.4 Hz, 1H), 1.20 (t, *J* = 6.8 Hz, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 175.36, 148.98, 139.24,

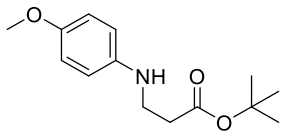
134.70, 131.61, 130.63, 130.44, 117.28, 111.98, 63.79, 53.40, 49.44, 16.74. **HRMS** (APCI$^+$, m/z) calculated for $C_{17}H_{19}BrNO_2$ [M+H]$^+$: 348.05992; found: 348.05973.

1-(4-bromophenyl)-3,3-dimethylazetidin-2-one (4ei)



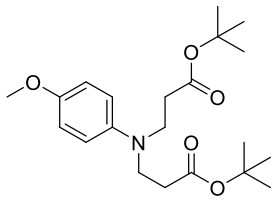
The compound was synthesized according to the literature procedure[50] using ethyl 3-((4-bromophenyl)amino)-2,2-dimethylpropanoate (300 mg, 1 mmol) and methylmagnesium bromide solution (119 mg, 1 mmol) to afford **4ei** (193 mg, 76% yield). Light yellow solid was obtained after column chromatography (SiO_2, Pentane/EtOAc 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 2H), 3.35 (s, 2H), 1.34 (s, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.60, 140.27, 134.65, 120.53, 118.67, 55.88, 52.89, 24.02. **HRMS** (APCI$^+$, m/z) calculated for $C_{11}H_{13}BrNO$ [M+H]$^+$: 254.01805; found: 254.01743.

***tert*-Butyl 3-((4-methoxyphenyl)amino)propanoate (3ia)**



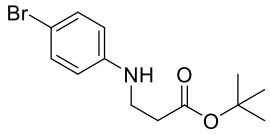
The compound was synthesized according to the **General procedure** using 4-methoxyaniline (61.5 mg, 0.5 mmol) and *tert*-butyl 3-hydroxypropanoate (146 mg, 1mmol) to afford **3ia** (22 mg, 18% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 90:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.78 (d, *J* = 9.2 Hz, 2H), 6.62 (d, *J* = 8.8 Hz, 2H), 3.75 (s, 3H), 3.35 (t, *J* = 6.4 Hz, 2H), 2.51 (t, *J* = 6.4 Hz, 2H), 1.45 (s, 9H).**^{13}C NMR** (151 MHz, $CDCl_3$): δ 171.95, 152.64, 141.81, 115.04, 114.97, 80.98, 55.92, 41.08, 35.16, 28.26. **HRMS** (APCI$^+$, m/z) calculated for $C_{14}H_{22}NO_3$ [M+H]$^+$: 252.15942; found: 252.15926.

Di-*tert*-butyl 3,3'-((4-methoxyphenyl)azanediyl)dipropionate (3ia^)



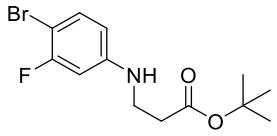
The compound was synthesized according to the **General procedure** using 4-methoxyaniline (61.5 mg, 0.5 mmol) and *tert*-butyl 3-hydroxypropanoate (146 mg, 1mmol) to afford **3ia^** (97 mg, 51% yield). Colorless oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 90:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.82 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 9.2 Hz, 2H), 3.74 (s, 3H), 3.49 (t, *J* = 7.2 Hz, 4H), 2.43 (t, *J* = 7.2 Hz, 4H), 1.43 (s, 18H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.66, 152.42, 141.87, 116.12, 114.94, 80.58, 55.77, 48.04, 33.89, 28.17. **HRMS** (APCI$^+$, m/z) calculated for $C_{21}H_{34}NO_5$ [M+H]$^+$: 380.24315; found: 380.24282.

tert-Butyl 3-((4-bromophenyl)amino)propanoate (3ii)



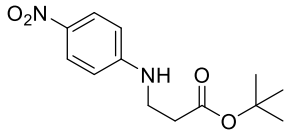
The compound was synthesized according to the **General procedure** using 4-bromoaniline (86 mg, 0.5 mmol) and *tert*-butyl 3-hydroxypropanoate (146 mg, 1mmol) to afford **3ii** (78 mg, 52% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 98:2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.51 (d, *J* = 8.8 Hz, 2H), 3.36 (t, *J* = 6.0 Hz, 2H), 2.51 (t, *J* = 6.4 Hz, 2H), 1.45 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 171.71, 146.73, 132.11, 114.88, 109.49, 81.18, 39.89, 34.92, 28.24. **HRMS** (APCI$^+$, m/z) calculated for $C_{13}H_{19}BrNO_2$ $[M+H]^+$: 300.05937; found: 300.05966.

tert-Butyl 3-((4-bromo-3-fluorophenyl)amino)propanoate (3ik)



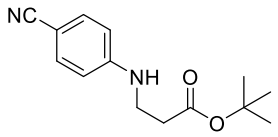
The compound was synthesized according to the **General procedure** using 4-bromo-3-fluoroaniline (95 mg, 0.5 mmol) and *tert*-butyl 3-hydroxypropanoate (146 mg, 1mmol) to afford **3ik** (114 mg, 72% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 98:2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27-7.23 (m, 1H), 6.40 (dd, *J* = 11.2 Hz, *J* = 2.4 Hz, 1H), 6.31 (dd, *J* = 8.4 Hz, *J* = 2.0 Hz, 1H), 3.35 (t, *J* = 6.4 Hz, 2H), 2.52 (t, *J* = 6.0 Hz, 2H), 1.45 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 171.57, 160.79, 159.17, 148.68, 148.61, 133.55, 133.53, 110.62, 101.09, 100.92, 95.41, 95.27, 81.37, 77.37, 77.16, 76.95, 39.86, 34.74, 28.24. **HRMS** (APCI$^+$, m/z) calculated for $C_{13}H_{18}BrFNO_2$ $[M+H]^+$: 318.04995; found: 318.01567.

tert-Butyl 3-((4-nitrophenyl)amino)propanoate (3im)



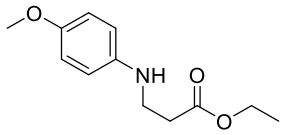
The compound was synthesized according to the **General procedure** using 4-nitroaniline (69 mg, 0.5 mmol) and *tert*-butyl 3-hydroxypropanoate (146 mg, 1mmol) to afford **3im** (78 mg, 59% yield). Bright yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 80:20). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 9.2 Hz, 2H), 6.54 (d, *J* = 9.2 Hz, 2H), 3.48 (t, *J* = 6.4 Hz, 2H), 2.55 (t, *J* = 6.4 Hz, 2H), 1.44 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.29, 153.07, 138.22, 126.53, 111.27, 81.59, 39.10, 34.74, 28.19. **HRMS** (APCI$^+$, m/z) calculated for $C_{13}H_{19}N_2O_4$ $[M+H]^+$: 267.13393; found: 267.13373.

tert-Butyl 3-((4-cyanophenyl)amino)propanoate (3io)



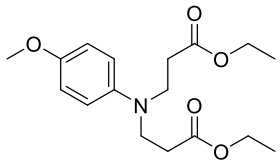
The compound was synthesized according to the **General procedure** using 4-aminobenzonitrile (59 mg, 0.5 mmol) and *tert*-butyl 3-hydroxypropanoate (146 mg, 1mmol) to afford **3io** (59 mg, 48% yield). Light yellow solid was obtained after column chromatography (SiO_2, Pentane/EtOAc 80:20). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.8 Hz, 2H), 6.57 (d, *J* = 8.8 Hz, 2H), 3.43 (t, *J* = 6.4 Hz, 2H), 2.53 (t, *J* = 6.4 Hz, 2H), 1.44 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.39, 150.95, 133.86, 120.45, 112.52, 99.18, 81.47, 39.01, 34.78, 28.21. **HRMS** (APCI$^+$, m/z) calculated for $C_{14}H_{19}N_2O_2$ $[M+H]^+$: 247.14410; found: 247.14387. The spectral data are identical to the previously reported.[57]

Ethyl 3-((4-methoxyphenyl)amino)propanoate (3ja)



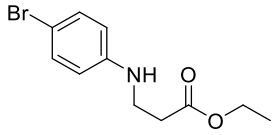
The compound was synthesized according to the **General procedure** using *p*-anisidine (37 mg, 0.3 mmol) and ethyl 3-hydroxypropanoate (71 mg, 0.6 mmol) to afford **3ja** (33 mg, 49% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 90:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.79 (d, *J* = 9.2 Hz, 2H), 6.62 (d, *J* = 8.8 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.75 (s, 3H), 3.40 (t, *J* = 6.4 Hz, 2H), 2.60 (t, *J* = 6.4 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H).**^{13}C NMR** (151 MHz, $CDCl_3$): δ 172.58, 152.62, 141.75, 115.06, 114.85, 60.73, 55.91, 40.79, 34.07, 14.34. **HRMS** (APCI$^+$, m/z) calculated for $C_{12}H_{18}NO_3$ $[M+H]^+$: 224.12812; found: 224.12810.

Diethyl 3,3'-((4-methoxyphenyl)azanediyl)dipropionate (3ja^)



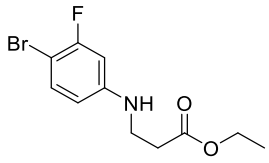
The compound was synthesized according to the **General procedure** using *p*-anisidine (37 mg, 0.3 mmol) and ethyl 3-hydroxypropanoate (71 mg, 0.6 mmol) to afford **3ja^** (54 mg, 56% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 90:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.83 (d, *J* = 9.2 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 4H), 3.75 (s, 3H), 3.53 (t, *J* = 7.2 Hz, 4H), 2.51 (t, *J* = 7.2 Hz, 4H), 1.24 (t, *J* = 7.2 Hz, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.35, 152.72, 141.67, 116.49, 115.00, 60.61, 55.82, 48.18, 32.79, 14.32. **HRMS** (APCI$^+$, m/z) calculated for $C_{17}H_{26}NO_5$ $[M+H]^+$: 324.18055; found: 324.18050.

Ethyl 3-((4-bromophenyl)amino)propanoate (3ji)



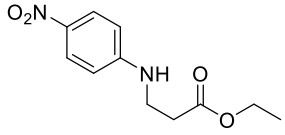
The compound was synthesized according to the **General procedure** using 4-bromoaniline (51 mg, 0.3 mmol) and ethyl 3-hydroxypropanoate (71 mg, 0.6 mmol) to afford **3ji** (45 mg, 55% yield). Light yellow oil was obtained after column chromatography (SiO_2, Pentane/EtOAc 90:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 8.8 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.40 (t, *J* = 6.4 Hz, 2H), 2.59 (t, *J* = 6.4 Hz, 2H), 1.26 (t, *J* = 6.8 Hz, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.35, 146.73, 132.09, 114.71, 109.37, 60.83, 39.55, 33.84, 14.31. **HRMS** (APCI$^+$, m/z) calculated for $C_{11}H_{15}BrNO_2$ $[M+H]^+$: 272.02602; found: 272.02581.

Ethyl 3-((4-bromo-3-fluorophenyl)amino)propanoate (3jk)



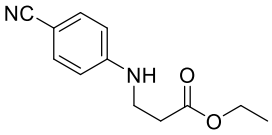
The compound was synthesized according to the **General procedure** using 4-bromo-3-fluoroaniline (57 mg, 0.3 mmol) and ethyl 3-hydroxypropanoate (71 mg, 0.6 mmol) to afford **3jk** (39 mg, 45% yield). Light yellow solid was obtained after column chromatography (SiO_2, Pentane/EtOAc 90:10). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24 (t, *J* = 8.4 Hz, 1H), 6.37 (dd, *J* = 11.2 Hz, *J* = 2.8 Hz, 1H), 6.28 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.39 (t, *J* = 6.0 Hz, 2H), 2.59 (t, *J* = 6.4 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H).**^{13}C NMR** (151 MHz, $CDCl_3$): δ 172.25, 159.98 (d, J_{CF} = 244.2 Hz), 148.74 (d, J_{CF} = 9.1 Hz), 133.53 (d, J_{CF} = 2.3 Hz), 110.38 (d, J_{CF} = 2.7 Hz), 100.77 (d, J_{CF} = 25.7 Hz), 95.11 (d, J_{CF} = 21.1 Hz), 60.95, 39.46, 33.68, 14.31. **HRMS** (APCI$^+$, m/z) calculated for $C_{11}H_{14}BrFNO_2$ $[M+H]^+$: 290.01865; found: 290.01876.

Ethyl 3-((4-nitrophenyl)amino)propanoate (3jm)



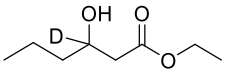
The compound was synthesized according to the **General procedure** using 4-nitroaniline (41 mg, 0.3 mmol) and ethyl 3-hydroxypropanoate (71 mg, 0.6 mmol) to afford **3jm** (36 mg, 51% yield). Yellow solid was obtained after column chromatography (SiO_2, Pentane/EtOAc 70:30). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 9.2 Hz, 2H), 6.55 (d, *J* = 9.2 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.54 (t, *J* = 6.0 Hz, 2H), 2.64 (t, *J* = 6.4 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H).**^{13}C NMR** (151 MHz, $CDCl_3$): δ 172.03, 152.86, 138.47, 126.59, 111.33, 61.17, 38.93, 33.64, 14.32. **HRMS** (APCI$^+$, m/z) calculated for $C_{11}H_{15}N_2O_4$ $[M+H]^+$: 239.10263; found: 239.10267.

Ethyl 3-((4-cyanophenyl)amino)propanoate (3jo)



The compound was synthesized according to the **General procedure** using 4-aminobenzonitrile (35 mg, 0.3 mmol) and ethyl 3-hydroxypropanoate (71 mg, 0.6 mmol) to afford **3jo** (34 mg, 52% yield). Light yellow semi-solid was obtained after column chromatography (SiO_2, Pentane/EtOAc 70:30). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 4.66 (*br* s, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.48 (t, *J* = 6.0 Hz, 2H), 2.61 (t, *J* = 6.0 Hz, 2H), 1.26 (t, *J* = 6.8 Hz, 3H).**^{13}C NMR** (151 MHz, $CDCl_3$): δ 172.08, 150.90, 133.88, 120.45, 112.42, 99.18, 61.03, 38.72, 33.67, 14.29. **HRMS** ($APCI^+$, m/z) calculated for $C_{12}H_{15}N_2O_2$ $[M+H]^+$: 219.11280; found: 219.11283.

Ethyl 3-hydroxyhexanoate-3-d (1b-d1)



The compound was synthesized according to the literature procedure.[58] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.12 (q, *J* = 7.2 Hz, 2H), 2.92 (*br* s, 1H), 2.44 (d, *J* = 16.4 Hz, 1H), 2.35 (d, *J* = 16.4 Hz, 1H), 1.50-1.29 (m, 4H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 173.01, 67.30 (t, *J* = 22.0 Hz), 60.58, 41.27, 38.54, 18.61, 14.13, 13.91.

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